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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ACTELION PHARMACEUTICALS LTD. and ACTELION CLINICAL RESEARCH, INC., Plaintiffs,	)	
v.	)	Case No. 1:12-cv-05743-NLH-AMD
APOTEX INC., APOTEX CORP., ROXANE LABORATORIES, INC., and ACTAVIS ELIZABETH LLC, Defendants.	)	

MEMORANDUM OF LAW IN SUPPORT OF PLAINTIFFS' MOTION FOR JUDGMENT ON THE PLEADINGS AND TO DISMISS COUNTERCLAIMS

Motion Day: March 18, 2013

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INTRODUCTION

The relief defendants/counterclaimants seek in this case is both extraordinary and unwarranted as a matter of law. Apotex Inc., Apotex Corporation (collectively, "Apotex"), Roxane Laboratories, Inc. ("Roxane") and Actavis Elizabeth LLC ("Actavis") ask this Court to force Actelion Pharmaceuticals Limited ("APL") and Actelion Clinical Research, Inc. ("ACR") (individually and collectively, "Actelion") to sell them samples of Actelion's patented drug, Tracleer. These potential generic competitors seek to compel such sales even though Actelion does not do business, has not done business and does not want to do business with them. Roxane also seeks to force Actelion to sell it another patented drug, Zavesca. The sole purpose of these proposed judicially-forced sales is to make it easier for the potential generic competitors to test and copy Actelion's products.

Such extreme relief would be unprecedented. The antitrust laws, upon which the generic competitors base their claims, do not obligate Actelion to sell its products (even samples) to firms with which it chooses not to deal or to assist potential rivals in entering the marketplace. As the Supreme Court explained in *Verizon Communications, Inc. v. Law Offices of Curtis V. Trinko, LLP*, the antitrust laws do not give rivals "*carte blanche* to insist that a[n alleged] monopolist alter its way of doing business whenever some other approach might yield greater competition." 540 U.S. 398, 415-16 (2004).

This principle applies with particular force here, where there is no history of dealing between the parties, the drug products at issue are patented, there are other paths to the marketplace available to the potential generic competitors, and the drugs pose significant health and safety risks requiring distribution restrictions as a condition of FDA approval. The potential generic competitors allege that access to Actelion's products is required for purposes of the

FDA's less-costly Abbreviated New Drug Application ("ANDA") process. However, even if Actelion were currently able to sell samples to its potential generic rivals unconstrained by the FDA-required restrictions, it is under no legal obligation to do so merely to assist those rivals in taking advantage of a regulatory shortcut.

The relevant facts are few and undisputed: APL developed Tracleer, a patent-protected drug which it markets in the United States through a U.S. affiliate. Tracleer can cause serious potential side effects. As a result, its distribution and sale are restricted by an FDA-mandated Risk Evaluation and Mitigation Strategy ("REMS").[1] Unable to buy Tracleer from downstream distributors because of the REMS, Apotex, Roxane, and Actavis have each demanded that Actelion sell it samples of Tracleer for purposes of bioequivalence testing in connection with anticipated ANDA applications. Actelion has exercised its right to refuse to do business with these companies.

The law is straightforward: Actelion is under no duty to deal with or assist its would-be generic competitors. This well-settled rule of law is subject to narrow and rare exceptions, none of which applies here. There can be no doubt about this because Congress has twice considered, and twice refused to enact, legislation that would change the law and require—or at least allow, in the most recent instance—companies such as Actelion to sell samples of drug products covered by REMS programs to competitors. The generic companies are attempting to circumvent Congress's decision by asking the Court to do precisely what Congress rejected: To force companies like Actelion to sell drug products to their potential rivals. But the law does not

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[1] A REMS is an FDA-approved strategy to manage a known or potential serious risk associated with a drug or biological product. (Compl. ¶ 17; *see* Apotex Countercl. ¶ 24; Roxane Countercl. ¶ 28; Actavis Countercl. ¶ 24).

impose such a duty. Actelion is therefore entitled to its requested declaratory judgment relief as a matter of law.

The counterclaims filed by Apotex, Roxane, and Actavis also fail as a matter of law. Actelion is under no duty to sell its patented products to potential competitors and its decision not to do so cannot give rise to antitrust liability.

FACTUAL BACKGROUND

A. Tracleer

Pulmonary arterial hypertension ("PAH") is a relatively rare and potentially fatal medical disorder in which elevated blood pressure in the arteries of the lungs causes the heart to work harder than normal. (Compl. ¶ 15; Actavis Countercl. ¶ 29). APL submitted a New Drug Application ("NDA") to the FDA for a new PAH treatment using the compound bosentan. (Compl. ¶ 15; Apotex Answer ¶ 15; Roxane Countercl. ¶ 46; Actavis Answer ¶ 15). Following FDA approval, Actelion, through its U.S. affiliate Actelion Pharmaceuticals US, Inc. ("APUS"), began marketing a treatment for PAH under the proprietary name Tracleer. (Compl. ¶ 15; Apotex Answer ¶ 15; Roxane Answer ¶ 15; Actavis Answer ¶ 15). Tracleer is patent-protected, covered by U.S. Patent No. 5,292,740. (Compl. ¶ 16; *see* Apotex Countercl. ¶ 29; Roxane Countercl. ¶ 52; Actavis Countercl. ¶ 27).

There are a number of potentially significant health risks to patients taking Tracleer which in turn also create liability, litigation, and reputational risks for Actelion. Indeed, Tracleer's label contains a "black box" warning, the most serious warning the FDA can require for a drug product. The potential side effects from taking Tracleer can include serious liver

damage and serious birth defects if taken during pregnancy. (Tracleer Label, Ex. A[2]; Compl. ¶ 17; Apotex Answer ¶ 17; Roxane Countercl. ¶ 9; Actavis Answer ¶ 17). These risks are sufficiently serious that the FDA required, as a condition of its approval, that distribution of Tracleer be limited under a REMS program.[3] (FDA, Tracleer Approval Letter, Nov. 20, 2001, Ex. B, *available at* www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-290_Tracleer_Approv.pdf).

In its letter approving Tracleer, the FDA reiterated to Actelion that the Tracleer REMS was "an important part of the postmarketing risk management for Tracleer." (*Id.*). The FDA listed nine requirements for the Tracleer REMS program because of the health risks associated with the drug, each of which highlights the importance of carefully managing and monitoring distribution and use of the drug. Among other things, the REMS requires that Tracleer be prescribed or dispensed only through pharmacies, practitioners, and health care settings that are specially certified and bound by contract to follow a strict protocol to monitor and protect patient health. (New Supplement for NDA 21-290, Tracleer REMS Modification, Jan. 31, 2010 ("Tracleer REMS") at 2-6, Ex. C). The protocol includes monthly follow-up with patients to ensure that liver function testing and pregnancy testing have been completed; that only a limited supply of Tracleer can be distributed at a time; that Tracleer can only be dispensed to patients

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2 In evaluating a motion under Federal Rule of Civil Procedure 12(c) or 12(b)(6), a court may consider the complaint, matters of public record, and authentic documents integral to the complaint without converting the motion to one for summary judgment. *Mayer v. Belichick*, 605 F.3d 223, 230 (3d Cir. 2010); *Mele v. Fed. Reserve Bank of N.Y.*, 359 F.3d 251, 256 n.5 (3d Cir. 2004).

3 Tracleer's risk mitigation program was originally required prior to the FDA's REMS initiative following the Food and Drug Administration Amendment Act of 2007. The program, called the Tracleer Access Program, was developed to address the FDA's safety concerns before Tracleer could be approved. The Tracleer Access Program subsequently became the approved REMS.

who are enrolled in the REMS program; and that certain defined patient counseling is completed regularly. (*Id.*). The REMS also requires that Actelion maintain data relating to adverse events, monitor prescription and distribution data, develop educational materials, and audit certified pharmacies to ensure compliance. (*Id.* at 6-7).

Actelion may not change the REMS program without obtaining FDA approval. (Tracleer Approval Letter at 2, Ex. B). Noncompliance with the REMS could lead to serious health and safety risks to patients as well as potential product liability litigation, reputational harm to Actelion, or penalties imposed by the FDA. *See* 21 U.S.C. §§ 352(y), 355(p).

B. Zavesca

Zavesca is the trade name for miglustat, a compound used to treat mild to moderate type 1 Gaucher disease in people who cannot be treated with enzyme replacement therapy. (Roxane Countercl. ¶ 57). Gaucher disease is a disorder in which the body does not produce enough of an enzyme to break down fatty substances. The build-up of fatty substances can cause serious problems in parts of the body such as the liver, spleen, lungs, and bones.

Actelion is the holder of the NDA for Zavesca. (*See* Roxane Countercl. ¶ 55). Because of the potential for serious birth defects if taken by pregnant women, Actelion developed, at FDA's request, a restricted distribution program which would provide the appropriate "risk/benefit ratio." (*See* FDA, Center for Drug Evaluation and Research, [Zavesca] Medical Review at 1, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-348_Zavesca_Medr_P1.pdf, Ex. D). The FDA approved Actelion's proposed distribution plan, and it approved Zavesca for the treatment of type 1 Gaucher disease in 2003. (*See* Roxane Countercl. ¶ 56).

Zavesca is a patent-protected drug. The FDA's Orange Book lists two patents covering Zavesca: U.S. Patent No. 5,472,969 and U.S. Patent No. 5,525,616. (Roxane Countercl. ¶ 62).

C. Requests for Samples

1. Apotex

On January 21, 2011, APUS, an affiliate of APL, received a letter from Apotex Inc. informing Actelion of Apotex's desire to file an ANDA seeking FDA approval to market a generic version of Actelion's patented Tracleer drug product. (Compl. ¶ 21; Apotex Answer ¶ 21; Jan. 21, 2011 Letter, Ex. E). Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness required in an NDA. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent to (i.e., performs in the same manner as) the innovator drug product. (Compl. ¶ 21; *see also* 21 U.S.C. § 355(j)).

In its January 21, 2011 letter, Apotex Inc. sought samples of Tracleer from APUS so that it could complete bioequivalency studies and submit an ANDA seeking FDA approval of a generic version of Actelion's Tracleer drug product. (Compl. ¶ 22; Jan. 21, 2011 Letter, Ex. E). Although the request was directed to APUS, any samples would actually be supplied by APL.

Actelion did not provide samples of Tracleer, and Apotex Inc. wrote again, repeating its demands for Tracleer samples and asserting that Actelion was legally required to fulfill Apotex Inc.'s request. (Compl. ¶¶ 23-25; Apr. 12, 2011 Letter, Ex. F; June 26, 2012 Letter, Ex. G; Aug. 1, 2012 Letter, Ex. H; Aug. 17, 2012 Letter, Ex. I; *see* Apotex Answer ¶¶ 23-25). In an August 1, 2012 letter, Apotex Inc. threatened litigation if its demands for samples were not met. (Compl. ¶ 25; Aug. 1, 2012 Letter, Ex. H). Apotex sent a draft complaint to Actelion, in which

Apotex sought a mandatory injunction and treble damages for an alleged antitrust violation. (Compl. ¶ 25; Aug. 1, 2012 Letter, Ex. H; *see* Apotex Answer ¶ 25).

Counsel for Actelion responded to Apotex's letters, affirming Actelion's right to choose with whom it does business and reminding Apotex of the restricted distribution required under the Tracleer REMS. (Compl. ¶¶ 24, 26; July 2, 2012 Letter, Ex. J; Aug. 9, 2012 Letter, Ex. K; Aug. 21, 2012 Letter, Ex. L; *see* Apotex Answer ¶¶ 24, 26).

2. Roxane

Roxane first demanded Tracleer tablets for the purpose of undertaking bioequivalence studies to support an ANDA for a generic version of Tracleer in early 2012. (Compl. ¶ 29; Roxane Answer ¶ 29; Jan. 12, 2012 Letter, Ex. M). Although Actelion responded to Roxane's demand and declined to sell to it, Roxane persisted in demanding Tracleer tablets. (*See* Compl. ¶¶ 30-31; Roxane Answer ¶¶ 30-31). In an August 1, 2012 letter, Roxane asserted that Actelion's refusal to sell it Tracleer violated the antitrust laws, and it threatened to file suit. (Compl. ¶ 31; Roxane Answer ¶ 31; Aug. 1, 2012 Letter, Ex. N). Counsel for Actelion again responded, reiterating Actelion's right to choose with whom it does business and how it structures its distribution system, and reminding Roxane of the strictures of the Tracleer REMS. (Compl. ¶ 32; Aug. 9, 2012 Letter, Ex. O; *see* Roxane Answer ¶ 32).

Roxane demanded a supply of Zavesca capsules from Actelion for the purpose of conducting bioequivalence studies for a generic version of Zavesca. (Roxane Countercl. ¶¶ 74-75; June 6, 2011 Letter, Ex. P). Actelion maintained its right to choose to whom it sells its products and declined to provide samples. (Roxane Countercl. ¶ 76).

3. Actavis

In a September 6, 2011 letter, Actavis demanded samples of Tracleer from Actelion for the purpose of bioequivalence testing. (Actavis Countercl. ¶ 34; Sept. 6, 2011 Letter, Ex. Q). Actelion declined, explaining that it had the right to choose with whom it does business. (Actavis Countercl. ¶ 35; Sept. 20, 2011 Letter, Ex. R).

D. Procedural History

Because of the persistent demands for samples and increasing threats of litigation, Actelion filed this action seeking a declaratory judgment that it has no legal duty or obligation to sell any quantity of Tracleer to generic competitors. (Doc. 1).

Apotex, Roxane, and Actavis each answered the Complaint and filed counterclaims against Actelion. Apotex has alleged that Actelion's decision not to supply it with Tracleer tablets violates Section 2 of the Sherman Act and Section 56:9-4 of the New Jersey Antitrust Act for unlawful monopolization and is a denial of an "essential facility." (Doc. 24, Apotex Countercl. Counts I, II, III, IV). Apotex has also alleged a state law claim for tortious interference. (Apotex Countercl. Count V). Apotex seeks the unusual and extraordinary remedy of a mandatory injunction requiring Actelion to supply Tracleer to it. (Apotex Countercl. Count VI).

Roxane has brought the same counterclaims as Apotex. (Doc. 25, Roxane Countercl. Counts I, III, VII, VIII, IX, X). In addition, Roxane—and no other counterclaimant—has alleged that Actelion's distribution arrangements violate Sections 1 and 2 of the Sherman Act and Section 56:9-3 of the New Jersey Antitrust Act. (Roxane Countercl. Counts I, V, VII). Roxane has also brought counterclaims with respect to Zavesca. (Roxane Countercl. Counts II, VI, VI).

Actavis has intervened in this case as a defendant and counterplaintiff. (Doc. 40). It answered Actelion's complaint and has alleged counterclaims that are identical to the counterclaims brought by Apotex. (Actavis Counter. Counts I-VII).

LEGAL ARGUMENT

I. ACTELION IS ENTITLED TO JUDGMENT AS A MATTER OF LAW.

Federal Rule of Civil Procedure 12(c) permits motions for judgment on the pleadings "[a]fter the pleadings are closed—but early enough not to delay trial." Fed. R. Civ. P. 12(c). A motion for judgment on the pleadings may be granted where there are no issues of material fact and the moving party is entitled to judgment as a matter of law. *Rosenau v. Unifund Corp.*, 539 F.3d 218, 221 (3d Cir. 2008).

Apotex, Roxane, and Actavis each answered the Complaint (Docs. 24, 25, 40) and the pleadings on Actelion's claim for declaratory relief are now closed. The pleadings demonstrate that there are no material facts in dispute. The parties agree that an Actelion entity markets the drug Tracleer in the United States (Compl. ¶ 15; Apotex Answer ¶ 15; Roxane Answer ¶ 15; Actavis Answer ¶15); that Tracleer is patent-protected (Compl. ¶ 16; Apotex Countercl. ¶ 29; Roxane Countercl. ¶ 52; Actavis Countercl. ¶ 27); that Tracleer may cause serious side effects (Compl. ¶ 17; Apotex Answer ¶ 17; Roxane Countercl. ¶ 9; Actavis Answer ¶ 17); and that Tracleer is subject to a REMS (Compl. ¶ 2; Apotex Answer ¶ 2; Roxane Answer ¶ 2; Actavis Answer ¶ 2). There is also no dispute that Apotex, Roxane, and Actavis each requested samples of Tracleer tablets for bioequivalence testing (Compl. ¶ 47; Apotex Answer ¶ 47; Roxane Answer ¶ 47; Actavis Countercl. ¶ 34); and that Actelion declined to provide, and has never provided, Tracleer to Apotex, Roxane, or Actavis (Compl. ¶¶ 41, 47; Apotex Answer ¶¶ 41, 47; Roxane Answer ¶¶ 41, 47; Actavis Countercl. ¶ 35). These undisputed facts make Actelion's

right to declaratory relief purely a question of law and one that may be properly addressed on a motion for judgment on the pleadings.

These same undisputed facts doom, as a matter of law, any right to relief on Apotex's, Roxane's, and Actavis's counterclaims. A motion to dismiss a counterclaim under Federal Rule of Civil Procedure 12(b)(6) should be granted when, taking the well-pleaded allegations as true, the court finds that the counterclaim fails to state a claim upon which relief can be granted. *See Seibert v. Quest Diagnostics Inc.*, No. 11-304, 2012 WL 1044308, at *8 (D.N.J. Mar. 28, 2012) (citing *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 555-56 (2007)). To avoid dismissal, a counterplaintiff must allege facts that allow a court to "draw the reasonable inference that the [counter]defendant is liable for the misconduct alleged." *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (citing *Twombly*, 550 U.S. at 556). None of the counterclaims here alleges any facts that would establish a duty on Actelion to do business with any counterclaimant, which is essential to any claim for relief as a matter of law. The counterclaims, therefore, should be dismissed with prejudice.

The same holds true for Roxane's counterclaims relating to Zavesca. The material facts surrounding Zavesca are undisputed. Actelion sells Zavesca through a U.S. affiliate (Roxane Countercl. ¶ 55); Zavesca is patent-protected (Roxane Countercl. ¶ 62); Zavesca may cause serious side effects (Roxane Countercl. ¶ 9); Zavesca is subject to a restricted distribution program (Roxane Countercl. ¶ 61); Roxane has requested samples of Zavesca from Actelion (Roxane Countercl. ¶¶ 74-76); and Actelion has never provided Zavesca to Roxane (Roxane Countercl. ¶¶ 74-76). The law does not obligate Actelion to sell Zavesca to Roxane, and Roxane's counterclaims should be dismissed for failure to state a claim.

A. Actelion Is Under No Duty to Supply Product to its Generic Competitors.

The antitrust laws do not impose a duty to deal with, or to assist, one's rivals. *United States v. Colgate & Co.*, 250 U.S. 300, 307 (1919). This principle has been repeatedly endorsed by the Supreme Court and by the courts of appeal. *Verizon Commc'ns Inc. v. Law Offices of Curtis V. Trinko, LLP*, 540 U.S. 398, 408 (2004); *see also Schor v. Abbott Labs.*, 457 F.3d 608, 610 (7th Cir. 2006) ("[A]ntitrust law does not require monopolists to cooperate with rivals by selling them products that would help the rivals to compete."); *Goldwasser v. Ameritech Corp.*, 222 F.3d 390, 400 (7th Cir. 2000) (the antitrust laws do not place an affirmative duty to assist rivals, "even on monopolists"); *Olympia Equip. Leasing Co. v. W. Union Tel. Co.*, 797 F.2d 370, 375-76 (7th Cir. 1986) (an alleged monopolist "has no general duty to help its competitors"); *Cal. Computer Prods., Inc. v. Int'l Bus. Machs. Corp.*, 613 F.2d 727, 744 (9th Cir. 1979) (holding that defendant was under no duty to "provide[] its rivals with disk products to examine and copy").

In *Trinko*, the plaintiff, a consumer of telecommunications services, claimed that Verizon violated the antitrust laws by failing to make elements of its network available to rivals. 540 U.S. at 404-04. The Court rejected the antitrust claim, and reiterated that the antitrust laws did not restrain Verizon's right "freely to exercise [its] own independent discretion as to parties with whom [it] will deal." *Id.* at 408 (citing *Colgate*, 250 U.S. at 307). As the Court explained further, antitrust law simply does not grant "*carte blanche* to insist that a monopolist alter its way of doing business whenever some other approach might yield greater competition." *Id.* at 415-16.

The analysis in *Goldwasser* is also particularly instructive. In that case, consumer plaintiffs claimed that Ameritech violated the antitrust laws by failing to assist its rivals in their

efforts to enter the market. 222 F.3d at 392. The *Goldwasser* court affirmed dismissal of the antitrust claims, despite the fact that, unlike here, Congress had imposed affirmative obligations on incumbent firms to assist new rivals (in the 1996 Telecommunications Act). The court explained that Ameritech had no ***antitrust*** duty to aid its competitors because such affirmative duties to aid rivals "do not exist under the unadorned antitrust laws." *Id.* at 400. The court further explained that a complaint—like the counterclaims in this case—"which takes the form 'X is a monopolist; X didn't help its competitors enter the market so that they could challenge its monopoly . . .'" does not state an antitrust claim "because the antitrust laws do not impose that kind of affirmative duty, even on monopolists." *Id.*

In contrast to the telecommunications markets, where Congress had created a regulatory regime that required incumbent providers to aid new entrants, Congress considered and expressly elected not to create a duty on branded companies to sell samples of products subject to REMS to potential ANDA filers.[4] The rule of law applicable in this case, as *Goldwasser* made clear, is the "unadorned" antitrust laws, which do not impose any duty to aid rivals.

This right to choose with whom to do business—and to choose not to do business with a rival—is a cornerstone of America's free enterprise system, and is consistent with basic free market principles. As a result, this right has been subject to exceedingly rare exceptions, where (1) the refusal is contrary to a prior course of dealing, or (2) the refusal relates to an "essential facility," although the viability of an independent exception under the so-called "essential

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[4] As discussed in Section I.B., *infra*, Congress twice considered legislation that would have required or merely allowed companies with drugs subject to REMS to provide samples to generic competitors. Both times, Congress chose not to enact the legislation.

facilities doctrine" is in doubt after *Trinko*. *Trinko*, 540 U.S. at 408 (noting that the Court had been "very cautious in recognizing such exceptions"). Neither of these exceptions applies here.

1. Actelion Never Supplied Tracleer or Zavesca to Apotex, Roxane, or Actavis.

The Supreme Court has recognized that, in very limited circumstances, there can be an exception to the rule that a unilateral refusal to deal by an alleged monopolist does not give rise to antitrust liability. For that exception to apply, however, there must have been a prior, profitable course of dealing between the parties, which the monopolist altered for no legitimate business reason. *Aspen Skiing Co. v. Aspen Highlands Skiing Corp.*, 472 U.S. 585 (1985). More recently, the Supreme Court emphasized that even such a refusal to deal reversing a prior course of dealing is "at or near the outer boundary of § 2 liability." *Trinko*, 540 U.S. at 409. Where, as here, the alleged monopolist has no prior history of dealing with the antitrust plaintiff, there can be no antitrust liability. *See Covad Commc'ns Co. v. BellSouth Corp.*, 374 F.3d 1044, 1049 (11th Cir. 2004) (affirming dismissal of claims where there was no history of voluntary course of dealing). As the court explained in *Covad Communications*, "*Trinko* now effectively makes the unilateral termination of a voluntary course of dealing a requirement for a valid refusal-to-deal claim under *Aspen*." *Id.*; *see also Eatoni Ergonomics, Inc. v. Research in Motion Corp.*, No. 11-5328-cv, 2012 WL 2348443, at *2-3 (2d Cir. June 21, 2012) (rejecting a refusal to deal claim where the parties "had no previous course of dealing"); *In re Elevator Antitrust Litig.*, 502 F.3d 47, 53 (2d Cir. 2007) (*Aspen Skiing* limited to cases in which "a monopolist seeks to terminate a prior (voluntary) course of dealing with a competitor").

Counterclaimants admit that Actelion has never supplied them with Tracleer or Zavesca. (*See* Compl. ¶ 41; Apotex Answer ¶ 41; Roxane Answer ¶ 41; Actavis Countercl. ¶ 35). Plainly,

Actelion's decision not to do business with its potential generic competitors does not fall within the very narrow exception described in *Aspen Skiing*.[5] This conclusion applies with particular force here where not only has Actelion never sold Tracleer or Zavesca to the generics, but the drugs at issue are patented. *See In re Indep. Serv. Orgs. Antitrust Litig.*, 203 F.3d 1322, 1326 (Fed. Cir. 2000) (rejecting antitrust liability for refusing to license patented technology absent circumstances involving sham patent litigation, unlawful tying, or fraud on the Patent & Trademark Office). Forcing Actelion to sell its patented products to the generics would vitiate the very underlying purpose of the Patent Act. *See id.*

Actelion is therefore entitled to a declaration that it has no duty to supply Apotex, Roxane, or Actavis with samples of Tracleer or Zavesca. For the same reasons, the counterclaims brought by Apotex and Actavis alleging monopolization (Apotex Countercl. Counts I, III; Actavis Countercl. Counts I, III) and by Roxane alleging monopolization and attempted monopolization (Roxane Countercl. Counts I, II, VII) fail as a matter of law and should be dismissed with prejudice.[6]

2. The Essential Facilities Doctrine Does Not Apply.

The generic competitors assert that Actelion should be forced to sell them products under the so-called "essential facilities doctrine," but that doctrine simply does not apply here. As a

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[5] In addition, the *Trinko* Court distinguished *Aspen Skiing* because in that case, the defendant refused to provide ski lift tickets, a product it sold at retail to the public, whereas in *Trinko*, the services at issue were not something generally available to the public. *Trinko*, 540 U.S. at 410. As in *Trinko*, Actelion does not make available or sell samples of its product for bioequivalence testing and defendants make no contrary allegation.

[6] In addition, as explained in connection with the essential facilities doctrine, the claims of the generic competitors that Actelion is under a duty to supply them with products fail for additional reasons as well—namely, that Tracleer and Zavesca are patented products and that there are alternative avenues to the marketplace for these competitors.

threshold matter, the Supreme Court in *Trinko* cast doubt on the validity of the essential facilities doctrine, stating that it was a "doctrine crafted by some lower courts" which the Supreme Court had never recognized. 540 U.S. at 410-11 ("We have never recognized such a doctrine."). Since *Trinko*, the validity of the essential facilities doctrine has been questioned. *See Pocono Invitational Sports Camp, Inc. v. Nat'l Collegiate Athletic Ass'n*, 317 F. Supp. 2d 569, 587 n.23 (E.D. Pa. 2004) (noting that *Trinko* called into question the use of the doctrine except in the most extreme cases); Daniel F. Spulber & Christopher S. Yoo, *Mandating Access to Telecom and the Internet: The Hidden Side of* Trinko, 107 COLUM. L. REV. 1822, 1869 & n.253 (2007) ("[C]ommentators generally acknowledge that [*Trinko's*] reasoning certainly casts serious doubts on the doctrine's continuing vitality.").

Even if the doctrine maintains some validity, it does not apply here. As a threshold matter, this case simply does not fit within the contours of the essential facilities doctrine. The doctrine arose in cases in which the defendant controlled access to some infrastructure or input that was necessary to compete in a ***different*** market with a ***different*** service or product. *See Otter Tail Power Co. v. United States*, 410 U.S. 366 (1973) (control of wholesale power allowed defendant to control access to downstream retail power supply); *United States v. Terminal R.R. Ass'n*, 224 U.S. 383 (1912) (control of railroad terminals and bridges extended control over railroad transportation services); *MCI Commc'ns Corp. v. Am. Tel. & Tel. Co.*, 708 F.2d 1081 (7th Cir. 1983) (control of local telephone services allowed defendant to control market for long distance telephone services). Where the doctrine has been applied, it has been to prevent a firm with monopoly power from extending that power "from one stage of production to another, and from one market into another." *MCI Commc'ns Corp.*, 708 F.2d at 1132.

The circumstances here are altogether different. There is no claim that Actelion controls access to a different market or that Actelion is attempting to extend market power "from one market into another." Rather, the generic rivals here claim that they require Actelion's products for the sole purpose of developing replicas to compete with Actelion ***in the very same markets*** in which the Actelion products themselves compete.

Moreover, there are two additional, independent reasons that the generic rivals cannot satisfy the individual elements of the essential facilities doctrine as a matter of law (for reasons which would be fatal to a claim under *Aspen Skiing* as well). In particular, patented products such as Tracleer and Zavesca cannot be considered essential facilities and there are alternative paths available to the marketplace for the generic competitors.

a. The Essential Facilities Doctrine Does Not Apply To Patented Products.

The essential facilities doctrine is inapplicable to patented products like Tracleer and Zavesca. *See Applera Corp. v. MJ Research, Inc.*, 349 F. Supp. 2d 338, 348 (D. Conn. 2004) ("To find a patent an 'essential facility' to which [a patent holder] must provide access would subvert the plain meaning and purpose of the Patent Act."); *Eatoni*, 2012 WL 2348443, at *3 (the essential facilities doctrine does not require a patent holder to share its patented mobile phones); *see also In re Indep. Serv. Orgs.*, 203 F.3d at 1326.

Eatoni, for example, is directly on point. Plaintiff there based its antitrust claim on an allegation that Research in Motion's ("RIM") "QWERTY" keyboard mobile phones were an essential facility. The court upheld dismissal of this claim, explaining that—even if RIM's mobile phones were the only compatible technology available to the plaintiff—antitrust law "does not obligate RIM to share its patented platform technology, from which RIM derives the

lawful power to exclude others." 2012 WL 2348443, at *3. Similarly, here, antitrust law does not require Actelion to share its patented drug products.

b. Competitors Are Free To Develop Competing Products.

A facility is not "essential" unless it is "vital to the claimant's competitive viability." *Monarch Entm't Bureau, Inc. v. N.J. Highway Auth.*, 715 F. Supp. 1290, 1300 (D.N.J. 1989); *see also Alaska Airlines, Inc. v. United Airlines, Inc.*, 948 F.2d 536, 544 (9th Cir. 1991) (a facility is essential only "if control of the facility carries with it the power to *eliminate* competition in the downstream market."). Where there are alternative means of competing, a facility is not essential.

Moreover, the mere fact that alternatives may be more expensive or less convenient does not support application of the essential facilities doctrine. *Eatoni*, 2012 WL 2348443, at *3 (RIM's keyboard not an essential facility because the plaintiff could work with other producers to make a "QWERTY" keyboard, although doing so might be less lucrative); *see also Midwest Gas Servs., Inc. v. Ind. Gas Co.*, 317 F.3d 703,714 (7th Cir. 2003) ("[T]he most economical route is not an essential facility when other routes are available.") (affirming dismissal of claim where more expensive alternatives existed). As the court in *Goldwasser* explained, although duplicating an incumbent's facilities might require a large investment, and take substantial time, such costs did not justify finding that the incumbent's facilities were essential. According to the *Goldwasser* court, "this is the normal way in which competitive markets work." 222 F.3d at 399.

There are alternative ways in which Apotex, Roxane, and Actavis can compete with Actelion. For example, the potential generic competitors here can develop drug products with the exact same formulation as Tracleer and, subject to intellectual property rights, file an NDA for FDA approval. Alternatively, depending on the formulations, they could also take advantage

of an FDA shortcut—an application under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act—that would allow them to make use of the FDA's previous finding of safety and efficacy. *See* 21 U.S.C. § 355(b)(2); 21 C.F.R. § 314.54. In addition, they could design a new formulation, using bosentan or another active ingredient, and file an NDA for that product. Similarly, any other company is free to develop a treatment for type 1 Gaucher disease, including products with the same formulation as Zavesca, submit an NDA or 505(b)(2) application for FDA approval, and then compete in the market with Zavesca.

In sum, for the reasons explained above, the essential facilities doctrine provides no basis upon which to deprive Actelion of its right to choose with whom to do business for a number of separate and independent reasons. Accordingly, Actelion is entitled to judgment as a matter of law and its declaratory relief should be granted. Counts II and IV of Apotex's counterclaims, Counts III, IV, and VII of Roxane's counterclaims, and Counts II and IV of Actavis's counterclaims should be dismissed with prejudice.

B. Congress Expressly Refused to Impose a Duty to Sell Samples On Companies Marketing Products Covered by REMS.

Congress explicitly considered imposing an affirmative duty to deal on manufacturers of products covered by REMS programs, but did not do so. Twice within the last five years, Congress considered legislation that would have required, or permitted, a manufacturer of a drug subject to a REMS to sell its product to competitors. In both instances, Congress made a deliberate judgment ***not to*** change the law by creating a duty to deal.

Pharmaceutical companies operate and bring products to market in a heavily regulated environment. Through the Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act ("FDCA"), Congress provided the ANDA shortcut mechanism. *See* 21 U.S.C. §

355(j). The Act generally allows generic drug manufacturers to skip the preclinical and clinical testing required of NDA filers and instead rely on a showing of bioequivalence with the innovator drug as the "reference listed drug." *See id.* Congress did not, however, include any requirement that a pharmaceutical innovator hand-deliver access to the shortcut by providing a generic competitor with samples for bioequivalence testing. It has always remained the business decision of the innovator company to choose with whom it does business. The existence of a REMS program does not change this principle.

Nothing in the REMS statute or related regulatory scheme requires an innovator company to give up rights it otherwise has, i.e., the right to choose with whom to deal, merely because its drug is subject to REMS restrictions.[7] The best proof of this is that Congress considered and rejected an explicit requirement forcing branded companies to supply generic competitors. In 2007, when Congress was considering the FDAAA, the House version of the bill included the following proposed language, which was omitted from the final version of the Act:

> (6) BIOEQUIVALENCE TESTING - Notwithstanding any other provisions in this subsection, the holder of an approved application that is subject to distribution restrictions required under this subsection that limit the ability of a sponsor seeking approval of [an ANDA] to purchase on the open market a sufficient quantity of drug to conduct bioequivalence testing shall provide to such a sponsor a sufficient amount of drug to conduct bioequivalence testing if the sponsor seeking approval [of an ANDA] (A) agrees to such restrictions on distribution as the Secretary finds necessary to assure safe use of the drug during

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[7] Apotex, Roxane, and Actavis mistakenly rely on a provision enacted as part of the Food and Drug Administration Amendment Act of 2007 ("FDAAA") that states: "No holder of an approved covered application shall use any element to assure safe use . . . to block or delay approval of an application under section 355(b)(2) or (j) . . . or to prevent application of such element . . . to a drug that is the subject of an [ANDA]." (Apotex Countercl. ¶ 25; Roxane Countercl. ¶ 29; Actavis Countercl. ¶ 26 (citing 21 U.S.C. § 355-1(f)(8))). There is nothing in this language, however, that requires Actelion to sell its products or that creates a duty to deal or to assist rival manufacturers.

> bioequivalence testing; and (B) pays the holder of the approved application the fair market value of the drug purchased for bioequivalence testing.

H.R. 2900, 110th Cong. § 901 (2007); *compare* 21 U.S.C. § 355-1.

Similar, but even less forceful, language was again rejected in 2012, when Congress considered the Food and Drug Administration Safety and Innovation Act ("FDASIA"). Language in the Senate amendment to the bill was merely permissive, not mandatory, but was nevertheless also excluded from the final version of the Act:

> (k) DRUG DEVELOPMENT AND TESTING.— (1) In General.— Notwithstanding any other provision of law, if a drug is a covered drug, no elements to ensure safe use shall prohibit, or be construed or applied to prohibit, supply of such drug to any eligible drug developer for the purpose of conducting testing necessary to support [an ANDA], if the Secretary has issued a written notice described in paragraph (2), and the eligible drug developer has agreed to comply with the terms of the notice.

S. 3187, 112th Cong. § 1331 (May 24, 2012).

Congress's rejections of these proposals demonstrates that there is no special exception to the general right to choose with whom to deal merely because a drug product is subject to restricted distribution in a REMS. *Cf. Russello v. United States*, 464 U.S. 16, 23 (1983) ("[I]t is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion [of statutory provisions].") (citation omitted); *Gulf Oil Corp. v. Copp Paving Co.*, 419 U.S. 186, 200 (1974) (where provisions in a bill are eliminated prior to passage, the change "strongly militates against a judgment that Congress intended a result that it expressly declined to enact"). The current legislation reflects Congress's consideration of the balance required between protecting intellectual property and other rights and in promoting competition. Accordingly, Actelion's right to choose whether or not it deals with a particular entity remains unchanged from the general principle that it has no duty to deal with or aid competitors.

C. The Generics' Allegations That They Could Satisfy the FDA-Required Distribution Restrictions Are Beside the Point.

The generics allege that they are able to satisfy the FDA-required restrictions on the distribution and use of Tracleer and Zavesca and, therefore, Actelion should be able to sell them samples regardless of those restrictions.[8] (Apotex Countercl. ¶¶ 41, 44; Roxane Countercl. ¶¶ 70-71; Actavis Countercl. ¶ 36). These allegations miss the point. Although Actelion's ability to sell samples of Tracleer and Zavesca to the generics is constrained by the FDA-required distribution restrictions, Actelion's right to choose not to do business with potential rivals exists independently of those restrictions. Consequently, even if the generics could comply with such restrictions—or if they did not exist—Actelion is still under no legal duty to sell them samples, as explained above.

Actelion is also under no conceivable obligation to take on faith the generics' assertions that they can comply with the FDA-required restrictions and to sell to them on that basis. Nor is Actelion under any legal obligation to engage in the substantial effort that would be required to confirm the generics' ability to comply. Similarly, Actelion should not be required to take on the burden of monitoring their continued compliance, as would be necessary to avoid the substantial risks to Actelion from generic non-compliance. Consequently, the generics' allegations that they would be able to comply with the applicable distribution restrictions does not alter the conclusion that, as a matter of law, Actelion is under no duty to deal with them.

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[8] Roxane also makes a half-hearted suggestion that the FDA has approved such sales generally, referring to an unidentified letter ostensibly from the FDA to an unnamed generic drug manufacturer in 2007. There is nothing, however, to suggest that this letter has anything to do with Tracleer or Zavesca.

D. The Counterclaims Brought By Apotex, Roxane, and Actavis Do Not State Claims That Raise a Right to Relief.

1. Federal Antitrust Claims

Even if Actelion were able to sell Tracleer and Zavesca to its potential generic rivals, their counterclaims fail as a matter of law. As set forth above, antitrust law does not impose a duty to deal with or aid competitors, even if a firm is a monopolist—a principle that applies with particular force where the products at issue are patented. Counts I and II of Apotex's Counterclaim, Counts I, II, III, and IV of Roxane's Counterclaim, and Counts I and II of Actavis's Counterclaim should be dismissed with prejudice for this reason alone.

Roxane alone alleges that Actelion's arrangements with distributors of Tracleer and Zavesca are a conspiracy in restraint of trade in violation of Section 1 of the Sherman Act and a conspiracy to monopolize in violation of Section 2 of the Sherman Act. (Roxane Countercls. Counts I, II, V, VI). These claims also fail as a matter of law and should be dismissed with prejudice.

A fundamental underlying element of a Section 1 claim, or a conspiracy claim under Section 2, is proof of an illegal agreement. *Queen City Pizza, Inc. v. Domino's Pizza, Inc.*, 124 F.3d 430, 442 (3d Cir. 1997); *Deborah Heart & Lung Ctr. v. Penn Presbyterian Med. Ctr.*, No. 11-cv-1290, 2011 WL 6935276, at *9 (D.N.J. Dec. 30, 2011). Roxane's claims fail because, as a matter of law, it cannot show that the distribution arrangements for Tracleer and Zavesca are illegal. Actelion's distribution arrangements with distributors of Tracleer and Zavesca are not only legal, they are currently ***required*** by the FDA for purposes of patient safety. *See* Tracleer Approval Letter at 2, Ex. C (requiring the "[d]istribution of Tracleer through a restricted distribution network"); Zavesca Medical Review at 1, Ex. E (noting that Actelion had agreed to a restricted distribution program for Zavesca to manage the risk/benefit ratio).

Moreover, Roxane's conspiracy claims fail for an additional reason as well, which is independent of the FDA-required restrictions. Actelion's arrangements for the distribution of its own patented products through wholesale distributors cannot lead to antitrust liability for conspiracy. To be illegal under the antitrust laws, an agreement must join "two independent sources of economic power previously pursuing separate interests." *Copperweld Corp. v. Ind. Tube Corp.*, 467 U.S. 752, 771 (1984). Although *Copperweld* involved parties in a parent/subsidiary relationship, it has been extended to "other parties with unified interests." *Shionogi Pharma, Inc. v. Mylan, Inc.*, No. Civ. A. 10-1077, 2011 WL 2550835, at *5 (D. Del. June 10, 2011). Under *Copperweld,* "coordinated activity by parties who lack independent sources of economic power and separate interests does not warrant scrutiny." *Levi Case Co. v. ATS Prods., Inc.*, 788 F. Supp. 428, 430 (N.D. Cal. 1992); *see also Shionogi*, 2011 WL 2550835, at *5.

In *Levi Case*, this principle led the court to dismiss a Section 1 claim based on an alleged conspiracy between a patent holder and its exclusive licensee, which manufactured and distributed the relevant products. According to the court, the defendants were not legally capable of conspiring for antitrust purposes because the "economic reality" was that they were not independent sources of economic power in the marketplace—absent their licensing and distribution relationship, they would not have been competitors. 788 F. Supp. at 431-32; *see also Shionogi*, 2011 WL 2550835, at *5 (dismissing claim alleging a conspiracy between a patent owner and its exclusive licensee responsible for marketing the relevant product).

Similarly, here, Actelion and its distributors are not independent sources of economic power, or independent sources of access to Tracleer and Zavesca. Like the licensee in *Levi Case*, the distributors participate in the sale of Tracleer and Zavesca only because of their appointment

by Actelion to sell its patented products. Roxane does not, and cannot, allege that, absent the distribution agreement with Actelion, the distributors would be competitors of Actelion or would be potential independent sources of Tracleer or Zavesca. As a result, nothing in the arrangement between Actelion and its distributors has deprived the market of independent, competing actors, as would be necessary to form an actionable conspiracy. *Levi Case Co.*, 788 F. Supp. at 431-32.

2. State Law Antitrust Claims

Because the New Jersey Antitrust Act is "virtually identical" to the Sherman Antitrust Act, it is construed in harmony with judicial interpretations of federal antitrust law. *St. Clair v. Citizens Fin. Group*, 340 F. App'x 62, 65 n.2 (3d Cir. 2009); N.J. Stat. Ann. § 56:9-18. Therefore, as the Sherman Act claims fail, so must the corresponding state law claims. Counts III and IV of Apotex's Counterclaim, Count VII of Roxane's Counterclaim, and Counts III and IV of Actavis's Counterclaim should be dismissed with prejudice.

3. Counterclaims Alleging Tortious Interference

Apotex, Roxane, and Actavis bring counterclaims alleging tortious interference with prospective economic advantage, alleging that Actelion's decision not to provide samples interfered with a prospective relationship with individuals suffering from PAH (Apotex), with suppliers (Roxane), or with unidentified "third parties" (Actavis). (Apotex Countercl. Count V; Roxane Countercl. Count VIII; Actavis Countercl. Count V). Roxane also alleges tortious interference with contractual relations. These claims fail as a matter of law.

Under New Jersey law, a counterplaintiff alleging tortious interference with prospective business relationships must demonstrate: (1) a reasonable expectation of economic benefit or advantage; (2) that the counterdefendant's actions were malicious, meaning that the harm was inflicted without justification or excuse; (3) a reasonable probability that the claimant would

have obtained the anticipated economic advantage; and (4) that the injury caused damage. *Syncsort Inc. v. Innovative Routines Int'l, Inc.*, No. 04-cv-3623, 2008 WL 1925304, at *19 (D.N.J. Apr. 30, 2008). To state a claim for tortious interference with contract, a counterplaintiff must show: (1) a contractual relationship; (2) interference with that contract, done intentionally and with malice; (3) the interference caused the loss; and (4) the interference caused damage. *DBA Distrib. Servs., Inc. v. All Source Freight Solutions, Inc.*, No. 11-cv-3901, 2012 WL 845929, at *6 (D.N.J. Mar. 13, 2012).

In both types of claims, the claimant must show that the alleged interference was done with malice, meaning that the harm was inflicted without justification or excuse. *Id.* The relevant inquiry is whether the conduct was sanctioned by "the rules of the game." *Id.* Where the "rules of the game" permit the challenged conduct, malice is absent and the claim is properly dismissed. *Id.* at 6-7; *Syncsort Inc.*, 2008 WL 1925304, at *19.

As established above, Actelion's actions have at all times been entirely lawful. Actelion has no obligation to supply its competitors with its products so that they might copy them and is free to—and, in this case, required to—arrange the distribution of its products to satisfy its regulatory obligations. Therefore, Actelion's conduct is well within the "rules of the game" and the counterclaims alleging tortious interference fail.[9]

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[9] In addition, for all of the reasons described above (among others), the counterclaimants are not entitled to injunctive relief. Therefore, Count VI of Apotex's Counterclaim, Count IX of Roxane's Counterclaim, and Count VI of Actavis's Counterclaim should be dismissed with prejudice.

CONCLUSION

For the foregoing reasons, Actelion's motion for judgment on the pleadings should be granted and Actelion's motion to dismiss the counterclaims should be granted.

January 16, 2012

Respectfully submitted,

s/ Michelle H. Yeary

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EXHIBIT A

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRACLEER safely and effectively. See full prescribing information for TRACLEER.

TRACLEER (bosentan) tablets, for oral use
Initial U.S. Approval: 2001

WARNING: RISKS OF HEPATOTOXICITY and TERATOGENICITY
See full prescribing information for complete boxed warning.

Tracleer is available only through a restricted distribution program called the Tracleer Access Program (T.A.P.) because of these risks (5.2):

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer (5.1).
- **Measure liver aminotransferases prior to initiation of treatment and then monthly (5.1).**
- **Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 x ULN (2.2, 5.1).**

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy (4.1, 8.1).
- **Must exclude pregnancy before and during treatment (4.1, 8.1).**
- **To prevent pregnancy, females of childbearing potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer (4.1, 8.1).**

RECENT MAJOR CHANGES

Dosage and Administration, Use in Females of Childbearing Potential (2.4)	Removal 10/2012
Warnings and Precautions (5.2, 5.6, 5.7)	10/2012

INDICATIONS AND USAGE

Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%) (1.1).

Considerations for use:
Consider whether benefits offset the risk of hepatotoxicity in WHO Class II patients. Early hepatotoxicity may preclude future use as disease progresses (1.1).

DOSAGE AND ADMINISTRATION

- Initiate at 62.5 mg twice daily with or without food for 4 weeks, and then increase to 125 mg twice daily (2.1).
- Patients with low body weight (<40 kg) and >12 years old: Initial and maintenance dose is 62.5 mg twice daily (2.3).
- Reduce the dose and closely monitor patients developing aminotransferase elevations >3 X ULN (2.2).
- Discontinue Tracleer 36 hours prior to initiation of ritonavir. Patients on ritonavir: Initiate Tracleer at 62.5 mg once daily or every other day (2.4).

DOSAGE FORMS AND STRENGTHS

- Tablet: 62.5 mg and 125 mg (3)

CONTRAINDICATIONS

- Pregnancy (4.1)
- Use with Cyclosporine A (4.2)
- Use with Glyburide (4.3)
- Hypersensitivity (4.4)

WARNINGS AND PRECAUTIONS

- Pre-existing hepatic impairment: Avoid use in moderate and severe impairment (5.3).
- Fluid retention: May require intervention (5.4).
- Pulmonary veno-occlusive disease (PVOD): If signs of pulmonary edema occur, consider the diagnosis of associated PVOD and consider discontinuing Tracleer (5.5)
- Decreased sperm counts (5.6)
- Decreases in hemoglobin and hematocrit: Monitor hemoglobin levels after 1 and 3 months of treatment, then every 3 months thereafter (5.7).

ADVERSE REACTIONS

Common adverse reactions (≥3% more than placebo) are respiratory tract infection and anemia (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Actelion at 1-866-228-3546 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Hormonal contraceptives: Tracleer use decreases contraceptive exposure and reduces effectiveness (7.2).
- Simvastatin and other CYP3A-metabolized statins: Combination use decreases statin exposure and may reduce efficacy (7.6).
- Rifampin: Alters bosentan exposure. Monitor hepatic function weekly for 4 weeks, followed by normal monitoring (7.7).

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Choose breastfeeding or Tracleer (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

WARNING: RISKS OF HEPATOTOXICITY and TERATOGENICITY

Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.). T.A.P. is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program. ***[see Warnings and Precautions (5.2)].***

Hepatotoxicity

In clinical studies, Tracleer caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious hepatotoxicity, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly ***[see Dosage and Administration (2.2), Warnings and Precautions (5.1)].*** **In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with Tracleer in patients with multiple comorbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded.**

In at least one case, the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction ***[see Dosage and Administration (2.2)].***

Elevations in aminotransferases require close attention ***[see Dosage and Administration (2.2)].*** **Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring for hepatotoxicity may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the reintroduction of Tracleer in these circumstances.**

Teratogenicity

Tracleer is likely to cause major birth defects if used by pregnant females based on animal data ***[see Use in Specific Populations (8.1)].*** **Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer** ***[see Drug Interactions (7.2)].*** **Obtain monthly pregnancy tests.**

1. INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%) *[see Clinical Studies (14.1)]*.

Considerations for use

Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of hepatotoxicity in WHO Class II patients, which may preclude future use as their disease progresses.

2. DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Tracleer must enroll in the Tracleer Access Program (T.A.P.) and must comply with the required monitoring to minimize the risks associated with Tracleer *[see Warnings and Precautions (5.2)]*.

2.1 Adult Dosage

Initiate treatment at 62.5 mg twice daily for 4 weeks and then increase to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of hepatotoxicity.

Tracleer should be administered in the morning and evening with or without food.

2.2 Dosage Adjustments for Patients Developing Aminotransferase Elevations

Measure liver aminotransferase levels prior to initiation of treatment and then monthly. If aminotransferase levels increase, revise the monitoring and treatment plan. The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations >3 X ULN during therapy with Tracleer. Discontinue Tracleer if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin $\geq$ 2 x ULN. There is no experience with the reintroduction of Tracleer in these circumstances.

Table 1: Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations >3 x ULN

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values, continue or reintroduce the treatment as appropriate*.
> 5 and ≤ 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values, consider reintroduction of the treatment*.
> 8 x ULN	Treatment should be stopped and reintroduction of Tracleer should not be considered. There is no experience with reintroduction of Tracleer in these circumstances.

* If Tracleer is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

2.3 Patients with Low Body Weight

In patients with a body weight below 40 kg but who are over 12 years of age, the recommended initial and maintenance dose is 62.5 mg twice daily. There is limited information about the safety and efficacy of Tracleer in children between the ages of 12 and 18 years *[see Use in Specific Populations (8.4)]*.

2.4 Use with Ritonavir

Coadministration of Tracleer in Patients on Ritonavir

In patients who have been receiving ritonavir for at least 10 days, start Tracleer at 62.5 mg once daily or every other day based upon individual tolerability *[see Drug Interactions (7.5)]*.

Coadministration of Ritonavir in Patients on Tracleer

Discontinue use of Tracleer at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume Tracleer at 62.5 mg once daily or every other day based upon individual tolerability *[see Dosage and Administration (2.6), Drug Interactions (7.5)]*.

2.5 Use in Patients with Pre-existing Hepatic Impairment

Tracleer should generally be avoided in patients with moderate or severe liver impairment. Initiation of Tracleer should generally be avoided in patients with elevated aminotransferases >3 x ULN. No dose adjustment is required in patients with mildly impaired liver function *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.6 Treatment Discontinuation

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered.

3. DOSAGE FORMS AND STRENGTHS

62.5 mg and 125 mg film-coated, tablets for oral administration.

62.5 mg tablets: round, biconvex, orange-white tablets, embossed with identification marking "62,5"

125 mg tablets: oval, biconvex, orange-white tablets, embossed with identification marking "125"

4. CONTRAINDICATIONS

4.1 Pregnancy

Use of Tracleer is contraindicated in females who are or may become pregnant. To prevent pregnancy, females of childbearing potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer . *[see Boxed Warning, Warnings and Precautions (5.2), Drug Interactions (7.2), Use in Specific Populations (8.1)]*.

4.2 Use with Cyclosporine A

Coadministration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Tracleer and cyclosporine A is contraindicated *[see Drug Interactions (7.3)]*.

4.3 Use with Glyburide

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore coadministration of glyburide and Tracleer is contraindicated *[see Drug Interactions (7.4)]*.

4.4 Hypersensitivity

Tracleer is contraindicated in patients who are hypersensitive to bosentan or any component of the product. Observed reactions include rash and angioedema *[see Adverse Reactions (6.2), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Elevations in ALT or AST by more than 3 x ULN were observed in 11% of Tracleer-treated patients (n = 658) compared to 2% of placebo-treated patients (n = 280). Three-fold increases were seen in 12% of 95 pulmonary arterial hypertension (PAH) patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥3 x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with Tracleer. The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 2x ULN) is a marker for potential serious hepatotoxicity.

Elevations of AST or ALT associated with Tracleer are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Tracleer.

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly and therapy adjusted accordingly *[see Dosage and Administration (2.2)]*. Discontinue Tracleer if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN.

5.2 Prescribing and Distribution Program for Tracleer

Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.) As a component of the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program. *[see Boxed Warning and Contraindications (4.1)]*.

Required components of the Tracleer REMS are:

- Healthcare professionals who prescribe Tracleer must review the prescriber educational materials, enroll in T.A.P. and comply with its requirements.
- Healthcare professionals must (1) review serum aminotransferases (ALT/AST) and bilirubin, and agree to order and monitor these tests monthly; and (2) for females of childbearing potential, confirm that the patient is not pregnant, and agree to order and monitor pregnancy tests monthly.
- To receive Tracleer, all patients must understand the risks and benefits, complete a patient enrollment form, and be re-enrolled annually by their prescriber.
- Pharmacies that dispense Tracleer must enroll in the program and agree to comply with the T.A.P. requirements.

Further information about Tracleer and T.A.P. is available at www.tracleerrems.com or 1-866-228-3546.

5.3 Patients with Pre-existing Hepatic Impairment

Tracleer is not recommended in patients with moderate or severe liver impairment. In addition, initiation of Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult *[see Boxed Warning, Dosage and Administration (2.5) Use in Specific Populations (8.6)]*.

5.4 Fluid Retention

Peripheral edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of Tracleer and other endothelin receptor antagonists. In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7 percent (placebo-corrected) of patients

In addition, there have been numerous postmarketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Tracleer or underlying heart failure, and the possible need for treatment or discontinuation of Tracleer. *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.

5.5 Pulmonary Veno-Occlusive Disease

Should signs of pulmonary edema occur, consider the possibility of associated pulmonary veno-occlusive disease and consider whether Tracleer should be discontinued.

5.6 Decreased Sperm Counts

Decreased sperm counts have been observed in patients receiving Tracleer. Preclinical data also suggest that Tracleer, like other endothelin receptor antagonists, may have an adverse effect on spermatogenesis *[see Adverse Reactions (6.1), Nonclinical Toxicology (13.1)]*.

5.7 Decreases in Hemoglobin and Hematocrit

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment *[see Adverse Reactions 6.1]*.

6. ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Fluid retention *[see Warnings and Precautions (5.4)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data on Tracleer were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 870 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg twice daily) were administered for a variety of durations. The exposure to Tracleer in these trials ranged from 1 day to 4.1 years (n=94 for 1 year; n=61 for 1.5 years and n=39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (n=328) to Tracleer ranged from 1 day to 1.7 years (n=174 more than 6 months and n=28 more than 12 months).

Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on Tracleer (6%; 15/258 patients) than on placebo (3%; 5/172 patients). In this database the only cause of discontinuations > 1% and occurring more often on Tracleer was abnormal liver function.

The adverse drug events that occurred in ≥3% of the Tracleer-treated patients and were more common on Tracleer in placebo-controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2:

Table 2. Adverse events* occurring in ≥3% of patients treated with Tracleer 125-250 mg twice daily and more common on Tracleer in placebo-controlled studies in pulmonary arterial hypertension

Adverse Event	Tracleer n = 258		Placebo n = 172	
	No.	%	No.	%
Respiratory Tract Infection	56	22%	30	17%
Headache	39	15%	25	14%
Edema	28	11%	16	9%
Chest Pain	13	5%	8	5%
Syncope	12	5%	7	4%
Flushing	10	4%	5	3%
Hypotension	10	4%	3	2%
Sinusitis	9	4%	4	2%
Arthralgia	9	4%	3	2%
Serum Aminotransferases, abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	-	

*Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.
Combined data from Study 351, BREATHE-1 and EARLY

Decreased Sperm Counts

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of Tracleer 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with Tracleer. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Tracleer was discontinued and after 2 months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Decreases in Hemoglobin and Hematocrit

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

The overall mean decrease in hemoglobin concentration for Tracleer-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of Tracleer treatment and hemoglobin levels stabilized by 4–12 weeks of Tracleer treatment. In placebo-controlled studies of all uses of Tracleer, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of Tracleer-treated patients and 3% of placebo-treated patients. In patients with PAH treated with doses of 125 and 250 mg twice daily, marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of Tracleer-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of Tracleer treatment.

During the course of treatment the hemoglobin concentration remained within normal limits in 68% of Tracleer-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

6.2 Postmarketing Experience

There have been several postmarketing reports of angioedema associated with the use of Tracleer. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing Tracleer.

The following additional adverse reactions have been reported during the postapproval use of Tracleer. Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

Unexplained hepatic cirrhosis *[see Boxed Warning]*

Liver failure *[see Boxed Warning]*

Hypersensitivity *[see Contraindications (4.4)]*

Thrombocytopenia

Rash

Jaundice

Anemia requiring transfusion

Neutropenia and leukopenia

7. DRUG INTERACTIONS

7.1 Cytochrome P450 Summary

Bosentan is metabolized by CYP2C9 and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with Tracleer will likely lead to large increases in plasma concentrations of bosentan. Coadministration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with Tracleer is not recommended.

Bosentan is an inducer of CYP3A and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when Tracleer is coadministered. Bosentan had no relevant inhibitory effect on any CYP isozyme in vitro (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A). Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

7.2 Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Tracleer is coadministered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer *[see Boxed Warning, Contraindications (4.1)]*.

An interaction study demonstrated that coadministration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.

7.3 Cyclosporine A

The concomitant administration of Tracleer and cyclosporine A is contraindicated *[see Contraindications (4.2)]*.

During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. Coadministration of bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A substrate) by approximately 50%.

7.4 Glyburide

An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of Tracleer and glyburide is contraindicated, and alternative hypoglycemic agents should be considered *[see Contraindications (4.3)]*.

Coadministration of bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of bosentan were also decreased by approximately 30%. Tracleer is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A. The possibility of worsened glucose control in patients using these agents should be considered.

7.5 Lopinavir/Ritonavir or Other Ritonavir-containing HIV Regimens

In vitro data indicate that bosentan is a substrate of the Organic Anion Transport Protein (OATP), CYP3A and CYP2C9. Ritonavir inhibits OATP and inhibits and induces CYP3A. However, the impact of ritonavir on the pharmacokinetics of bosentan may largely result from its effect on OATP.

In normal volunteers, coadministration of Tracleer 125 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily increased the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold and 5-fold, respectively, compared with those measured after Tracleer administered alone. Therefore, adjust the dose of Tracleer when initiating lopinavir/ritonavir *[see Dosage and Administration (2.4)]*.

Coadministration of bosentan 125 mg twice daily had no substantial impact on the pharmacokinetics of lopinavir/ritonavir 400/100 mg twice daily.

7.6 Simvastatin and Other Statins

Coadministration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Tracleer is also expected to reduce plasma concentrations of other statins that are significantly metabolized by CYP3A, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be

considered. Patients using CYP3A-metabolized statins should have cholesterol levels monitored after Tracleer is initiated to see whether the statin dose needs adjustment.

7.7 Rifampin

Coadministration of bosentan and rifampin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose (likely due to inhibition of OATP by rifampin), but about a 60% decrease in bosentan levels at steady-state. The effect of Tracleer on rifampin levels has not been assessed. When consideration of the potential benefits, and known and unknown risks leads to concomitant use, measure serum aminotransferases weekly for the first 4 weeks before reverting to normal monitoring.

7.8 Tacrolimus

Coadministration of tacrolimus and Tracleer has not been studied in humans. Coadministration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and Tracleer are used together.

7.9 Ketoconazole

Coadministration of bosentan 125 mg twice daily and ketoconazole, a potent CYP3A inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold in normal volunteers. No dose adjustment of Tracleer is necessary, but increased effects of Tracleer should be considered.

7.10 Warfarin

Coadministration of bosentan 500 mg twice daily for 6 days in normal volunteers decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of Tracleer and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among Tracleer- and placebo-treated patients.

7.11 Digoxin, Nimodipine, and Losartan

Bosentan has no significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of bosentan.

7.12 Sildenafil

In normal volunteers, coadministration of multiple doses of 125 mg twice daily bosentan and 80 mg three times daily sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. The changes in plasma concentrations were not considered clinically relevant and dose

adjustments are not necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

7.13 Iloprost

In a small, randomized, double-blind, placebo-controlled study, 34 patients treated with bosentan 125 mg twice daily for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 mcg 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations per day was 5.6.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X: Teratogenic Effects *[see Contraindications (4.1)]*

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well-controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. Bosentan caused teratogenic effects in animals including malformations of the head, mouth, face, and large blood vessels. If Tracleer is used during pregnancy or if a patient becomes pregnant while taking Tracleer, the patient should be apprised of the potential hazard to the fetus.

Females of childbearing potential should have a negative pregnancy test before starting treatment with Tracleer. The prescriber should not dispense a prescription for Tracleer without documenting a negative urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus.

Drug interaction studies show that bosentan reduces serum levels of the estrogen and progestin in oral contraceptives. Based on these findings, hormonal contraceptives (including oral, injectable, transdermal, and implantable contraceptives) may be less effective for preventing pregnancy in patients using Tracleer and should not be used as a patient's only contraceptive method *[see Drug Interactions (7.2)]*. Females of childbearing potential using Tracleer must use two reliable forms of contraception unless she has a tubal sterilization or has a Copper T 380A IUD or LNg 20 IUS. In these cases, no additional contraception is needed. Contraception should be continued until one month after completing Tracleer therapy. Females of childbearing potential using Tracleer should seek contraception counseling from a gynecologist or other expert as needed.

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose [MRHD] (on a mg/ m^2 basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased

stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m^2 basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs *[see Nonclinical Toxicology (13.1)]*.

8.3 Nursing mothers

It is not known whether bosentan is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from bosentan, a decision should be made to discontinue nursing or to discontinue Tracleer, taking into account the importance of Tracleer to the mother.

8.4 Pediatric use

Safety and efficacy in pediatric patients have not been established.

8.5 Geriatric use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. The pharmacokinetics of Tracleer has not been evaluated in patients with severe liver impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the systemic exposures to bosentan and its active metabolite increased significantly. Tracleer should generally be avoided in patients with moderate or severe liver impairment. Pharmacokinetics of bosentan was not altered in patients with mild impairment of hepatic function (Child-Pugh Class A) *[see Dosage and Administration (2.5), Warnings and Precautions (5.3), Pharmacokinetics (12.3)]*.

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment *[see Pharmacokinetics (12.3)]*.

10. OVERDOSAGE

Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg twice daily of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no

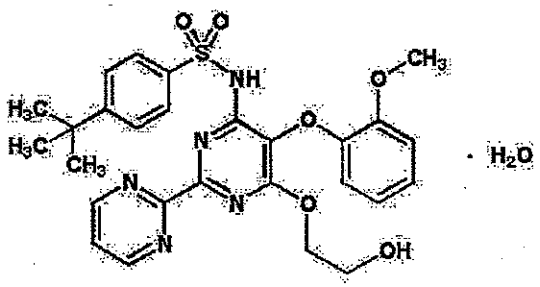
serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed.

In the postmarketing period, there was one reported overdose of 10,000 mg of Tracleer taken by an adolescent male patient. He had symptoms of nausea, vomiting, hypotension, dizziness, sweating, and blurred vision. He recovered within 24 hours with blood pressure support.

Bosentan is unlikely to be effectively removed by dialysis due to the high molecular weight and extensive plasma protein binding.

11. DESCRIPTION

Tracleer is the proprietary name for bosentan, an endothelin receptor antagonist that belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. It is designated chemically as 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2']-bipyrimidin-4-yl]- benzenesulfonamide monohydrate and has the following structural formula:



Bosentan has a molecular weight of 569.64 and a molecular formula of $C_{27}H_{29}N_5O_6S \cdot H_2O$. Bosentan is a white to yellowish powder. It is poorly soluble in water (1.0 mg/100 mL) and in aqueous solutions at low pH (0.1 mg/100 mL at pH 1.1 and 4.0; 0.2 mg/100 mL at pH 5.0). Solubility increases at higher pH values (43 mg/100 mL at pH 7.5). In the solid state, bosentan is very stable, is not hygroscopic and is not light sensitive.

Tracleer is available as 62.5 mg and 125 mg film-coated tablets for oral administration, and contains the following excipients: corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropylmethylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, and ethylcellulose. Each Tracleer 62.5 mg tablet contains 64.541 mg of bosentan, equivalent to 62.5 mg of anhydrous bosentan. Each Tracleer 125 mg tablet contains 129.082 mg of bosentan, equivalent to 125 mg of anhydrous bosentan.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. Bosentan has a slightly higher affinity for ET_A receptors than for ET_B receptors. The clinical impact of dual endothelin blockage is unknown.

Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease.

12.3 Pharmacokinetics

General

After oral administration, maximum plasma concentrations of bosentan are attained within 3–5 hours and the terminal elimination half-life ($t_{1/2}$) is about 5 hours in healthy adult subjects. The exposure to bosentan after intravenous and oral administration is about 2-fold greater in adult patients with pulmonary arterial hypertension than in healthy adult subjects.

Absorption and Distribution

The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food. The volume of distribution is about 18 L. Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

Metabolism and Elimination

Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10%–20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A and possibly also of CYP2C19. Total clearance after a single intravenous dose is about 4 L/hr in patients with pulmonary arterial hypertension. Upon multiple oral dosing, plasma concentrations in healthy adults decrease gradually to 50-65% of those seen after single dose administration, probably the effect of auto-induction of the metabolizing liver enzymes. Steady-state is reached within 3-5 days. Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine.

Special Populations

It is not known whether bosentan's pharmacokinetics is influenced by gender, race, or age.

Hepatic Impairment

In vitro and *in vivo* evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure of bosentan. In a study comparing 8 patients with mild liver impairment (Child-Pugh Class A) to 8 controls, the single- and multiple-dose pharmacokinetics of bosentan was not altered in patients with mild hepatic impairment.

In another small (N=8) pharmacokinetic study, the steady-state AUC of bosentan was on average 4.7 times higher and the active metabolite Ro 48-5033 was 12.4 times higher in 5 patients with moderately impaired liver function (Child-Pugh Class B) and pulmonary arterial hypertension associated with portal hypertension than in 3 patients with normal liver function and pulmonary arterial hypertension of other etiologies.

The pharmacokinetics of Tracleer has not been evaluated in patients with severe liver impairment (Child-Pugh Class C) *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), Use in Specific Populations (8.6)]*.

Renal Impairment

In patients with severe renal impairment (creatinine clearance 15–30 mL/min), plasma concentrations of bosentan were essentially unchanged and plasma concentrations of the three metabolites were increased about 2-fold compared to people with normal renal function. These differences do not appear to be clinically important.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg twice daily, on a mg/m^2 basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses ≥60 mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

Impairment of Fertility/Testicular Function

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m^2 basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/ day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

14. CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension

WHO Functional Class III-IV

Two randomized, double-blind, multi-center, placebo-controlled trials were conducted in 32 and 213 patients. The larger study (BREATHE-1) compared 2 doses (125 mg twice daily and 250 mg twice daily) of Tracleer with placebo. The smaller study (Study 351) compared 125 mg twice daily with placebo. Patients had severe (WHO functional Class III–IV) pulmonary arterial hypertension: idiopathic or heritable pulmonary arterial hypertension (72%) or pulmonary arterial hypertension associated with scleroderma or other connective tissue diseases (21%), or to autoimmune diseases (7%). There were no patients with pulmonary arterial hypertension associated with other conditions such as HIV disease or recurrent pulmonary emboli.

In both studies, Tracleer or placebo was added to patients' current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, and vasodilators (e.g., calcium channel blockers, ACE inhibitors), but not epoprostenol. Tracleer was given at a dose of 62.5 mg twice daily for 4 weeks and then at 125 mg twice daily or 250 mg twice daily for either 12 (BREATHE-1) or 8 (Study 351) additional weeks. The primary study endpoint was 6-minute walk distance. In addition, symptoms and functional status were assessed. Hemodynamic measurements were made at 12 weeks in Study 351.

The mean age was about 49 years. About 80% of patients were female, and about 80% were Caucasian. Patients had been diagnosed with pulmonary hypertension for a mean of 2.4 years.

Submaximal Exercise Ability

Results of the 6-minute walk distance at 3 months (Study 351) or 4 months (BREATHE-1) are shown in Table 3.

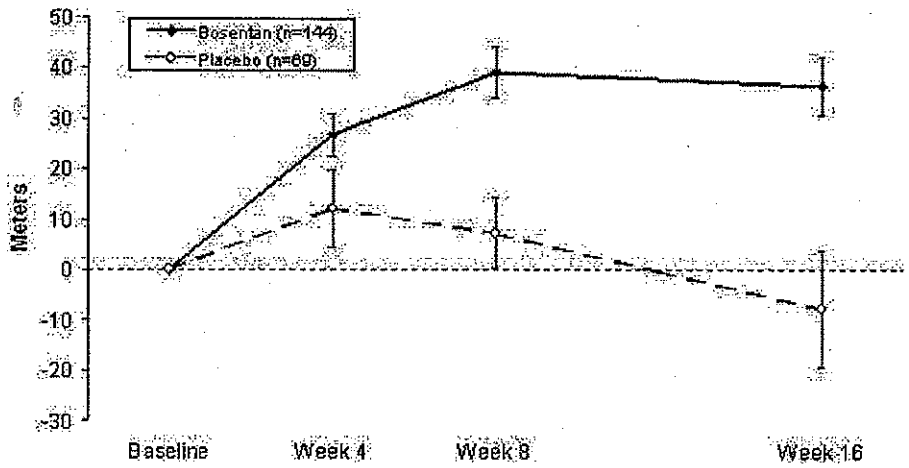
Table 3. Effects of Tracleer on 6-minute walk distance

	BREATHE-1			Study 351	
	Tracleer 125 mg twice daily (n = 74)	Tracleer 250 mg twice daily (n = 70)	Placebo (n = 69)	Tracleer 125 mg twice daily (n = 21)	Placebo (n = 11)
Baseline	326 ± 73	333 ± 75	344 ± 76	360 ± 86	355 ± 82
End point	353 ± 115	379 ± 101	336 ± 129	431 ± 66	350 ± 147
Change from baseline	27 ± 75	46 ± 62	-8 ± 96	70 ± 56	-6 ± 121
Placebo – subtracted	35 [a]	54 [b]		76 [c]	

Distance in meters: mean ± standard deviation. Changes are to week 16 for BREATHE-1 and to week 12 for Study 351.
[a]p=0.01; by Wilcoxon; [b]p=0.0001; by Wilcoxon; [c]p=0.02; by Student's t-test.

In both trials, treatment with Tracleer resulted in a significant increase in exercise ability. The improvement in walk distance was apparent after 1 month of treatment (with 62.5 mg twice daily) and fully developed by about 2 months of treatment (Figure 1). It was maintained for up to 7 months of double-blind treatment. Walking distance was somewhat greater with 250 mg twice daily, but the potential for increased hepatotoxicity causes this dose not to be recommended *[see Dosage and Administration (2.1)]*. There were no apparent differences in treatment effects on walk distance among subgroups analyzed by demographic factors, baseline disease severity, or disease etiology, but the studies had little power to detect such differences.

Figure 1. Mean Change in 6-min Walk Distance (BREATHE-1)



Change from baseline in 6-minute walking distance from start of therapy to week 16 in the placebo and combined Tracleer (125 mg twice daily and 250 mg twice daily) groups. Values are expressed as mean ± standard error of the mean.

Hemodynamic Changes

Invasive hemodynamic parameters were assessed in Study 351. Treatment with Tracleer led to a significant increase in cardiac index (CI) associated with a significant

reduction in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and mean right atrial pressure (RAP) (Table 4).

The relationship between hemodynamic effects and improvements in 6-minute walk distance is unknown.

Table 4: Change from Baseline to Week 12: Hemodynamic Parameters

	Tracleer 125 mg twice daily		Placebo
Mean CI (L/min/m^2)	n=20		n=10
Baseline	2.35±0.73		2.48±1.03
Absolute Change	0.50±0.46		-0.52±0.48
Treatment Effect		1.02[a]	
Mean PAP (mmHg)	n=20		n=10
Baseline	53.7±13.4		55.7±10.5
Absolute Change	-1.6±5.1		5.1±8.8
Treatment Effect		-6.7[b]	
Mean PVR (dyn•sec•cm^{-5})	n=19		n=10
Baseline	896±425		942±430
Absolute Change	-223±245		191±235
Treatment Effect		-415[a]	
Mean RAP (mmHg)	n=19		n=10
Baseline	9.7±5.6		9.9±4.1
Absolute Change	-1.3±4.1		4.9±4.6
Treatment Effect		-6.2[a]	

Values shown are means ± SD
[a]$p \leq 0.001$; [b]$p < 0.02$

Symptoms and Functional Status

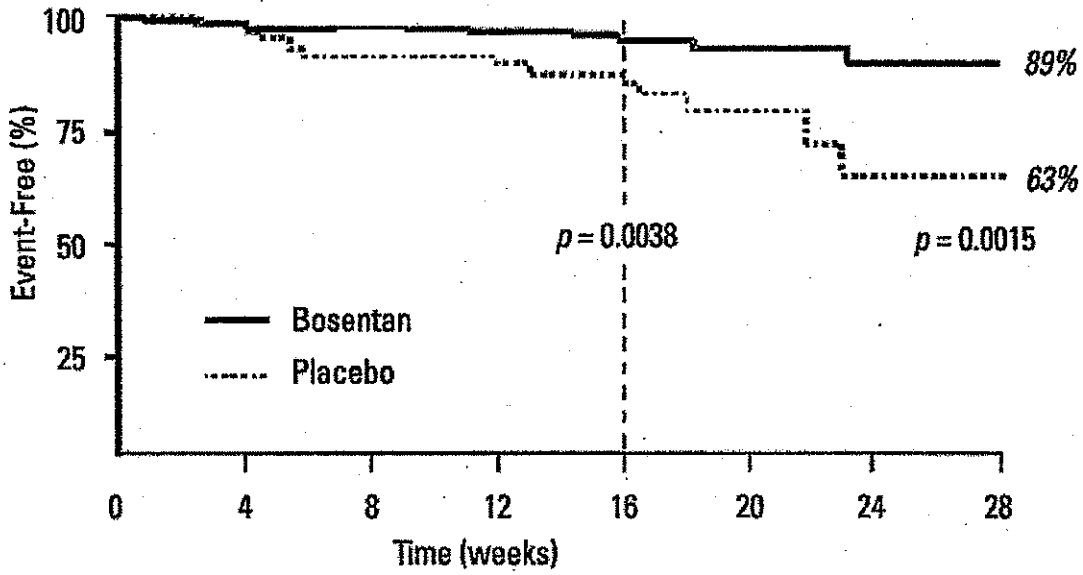
Symptoms of pulmonary arterial hypertension were assessed by Borg dyspnea score, WHO functional class, and rate of "clinical worsening." Clinical worsening was assessed as the sum of death, hospitalizations for PAH, discontinuation of therapy because of PAH, and need for epoprostenol. There was a significant reduction in dyspnea during walk tests (Borg dyspnea score), and significant improvement in WHO functional class in Tracleer-treated patients. There was a significant reduction in the rate of clinical worsening (Table 5 and Figure 2). Figure 2 shows the log-rank test reflecting clinical worsening over 28 weeks.

Table 5: Incidence of Clinical Worsening, Intent To Treat Population

	BREATHE-1		Study 351	
	Tracleer 125/250 mg twice daily (n = 144)	Placebo (n = 69)	Tracleer 125 mg twice daily (n = 21)	Placebo (n = 11)
Patients with clinical worsening [n (%)]	9 (6%)[a]	14 (20%)	0 (0%)[b]	3 (27%)
Death	1 (1%)	2 (3%)	0 (0%)	0 (0%)
Hospitalization for PAH	6 (4%)	9 (13%)	0 (0%)	3 (27%)
Discontinuation due to worsening of PAH	5 (3%)	6 (9%)	0 (0%)	3 (27%)
Receipt of epoprostenol[c]	4 (3%)	3 (4%)	0 (0%)	3 (27%)

Note: Patients may have had more than one reason for clinical worsening.
[a]p=0.0015 vs. placebo by log-rank test. There was no relevant difference between the 125 mg and 250 mg twice daily groups.
[b]p=0.033 vs. placebo by Fisher's exact test.
[c]Receipt of epoprostenol was always a consequence of clinical worsening.

Figure 2. Time to Clinical Worsening (BREATHE-1)



Time from randomization to clinical worsening with Kaplan-Meier estimate of the proportions of failures in BREATHE-1. All patients (n=144 in the Tracleer group and n=69 in the placebo group) participated in the first 16 weeks of the study. A subset of this population (n=35 in the Tracleer group and 13 in the placebo group) continued double-blind therapy for up to 28 weeks.

WHO Functional Class II

In a randomized, double-blind, multicenter, placebo-controlled trial, 185 mildly symptomatic PAH patients with WHO Functional Class II (mean baseline 6-minute walk distance of 443 meters) received Tracleer 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily (n = 93), or placebo (n = 92) for 6 months. Enrolled patients were treatment-naïve (n = 156) or on a stable dose of sildenafil (n = 29). The coprimary endpoints were change from baseline to month 6 in PVR and 6-minute walk distance. Time to clinical worsening (assessed as the sum of death, hospitalization due to PAH complications, or symptomatic progression of PAH), Borg dyspnea index, change in WHO functional class and hemodynamics were assessed as secondary endpoints.

Compared with placebo, Tracleer treatment was associated with a reduced incidence of worsening of at least one functional class (3% Tracleer vs. 13% placebo, $p = 0.03$), and improvement in hemodynamic variables (PVR, mPAP, TPR, cardiac index, and SVO_2; $p < 0.05$). The + 19 m mean (+14 m median) increase in 6-minute walk distance with Tracleer *vs.* placebo was not significant ($p = 0.08$). There was a significant delay in time to clinical worsening (first seen primarily as symptomatic progression of PAH) with Tracleer compared with placebo (hazard ratio 0.2, $p = 0.01$). Findings were consistent in strata with or without treatment with sildenafil at baseline.

Long-term Treatment of PAH

Long-term follow-up of patients with Class III and IV PAH who were treated with Tracleer in open-label extensions of trials (N=235) showed that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment.

These uncontrolled observations do not allow comparison with a group not given Tracleer and cannot be used to determine the long-term effect of Tracleer on mortality.

Pulmonary Arterial Hypertension related to Congenital Heart Disease with Left-to-Right Shunts

A small study (N=54) and its open label extension (N=37) of up to 40 weeks with patients with Eisenmenger physiology demonstrated effects of Tracleer on exercise and safety that were similar to those seen in other trials in patients with PAH (WHO Group 1).

14.2 Lack of Benefit in Congestive Heart Failure

Tracleer is not effective in the treatment of congestive heart failure with left ventricular dysfunction. In a pair of studies, 1613 subjects with NYHA Class III-IV heart failure, left ventricular ejection fraction <35%, on diuretics, ACE inhibitor, and other therapies, were randomized to placebo or Tracleer (62.5 mg twice daily titrated as tolerated to 125 mg twice daily) and followed for up to 70 weeks. Use of Tracleer was associated with no benefit on patient global assessment (the primary end point) or mortality. However, hospitalizations for heart failure were more common during the first 4 to 8 weeks after Tracleer was initiated. In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

16. HOW SUPPLIED/STORAGE AND HANDLING

62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62,5", packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap or in foil blister-strips for hospital unit-dosing.

NDC 66215-101-06: Bottle containing 60 tablets.

NDC 66215-101-03: Carton of 30 tablets in 10 blister strips of 3 tablets.

125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125", packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap or in foil blister-strips for hospital unit-dosing.

NDC 66215-102-06: Bottle containing 60 tablets.

NDC 66215-102-03: Carton of 30 tablets in 10 blister strips of 3 tablets.

Store at 20°C – 25°C (68°F – 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].

Manufactured for:

Actelion Pharmaceuticals US, Inc.

South San Francisco, CA 94080, USA

ACT20121004

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Restricted access

Advise the patient that Tracleer is only available through a restricted access program called the Tracleer Access Program (T.A.P.)

As a component of the Tracleer REMS, prescribers must review the contents of the Tracleer Medication Guide with the patient before initiating Tracleer.

Instruct patients that the risks associated with Tracleer include:

- **Hepatotoxicity**

  Discuss with the patient the requirement to measure serum aminotransferases monthly.

- **Serious birth defects if used by pregnant women**

  Educate and counsel female patients of child bearing potential about the need to use reliable methods of contraception during treatment with Tracleer and for one month after treatment discontinuation. Females of childbearing potential must have monthly pregnancy tests and must use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNg 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Advise the patient that Tracleer is available only from specialty pharmacies that are enrolled in Tracleer Access Program.

Patients must sign the Tracleer Enrollment for Patients and Prescribers form to confirm that they understand the risks of Tracleer.

Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the Tracleer REMS.

Other Risks Associated with Tracleer

Instruct patients that the risks associated with Tracleer also include the following:

Decreases in hemoglobin and hematocrit – advise patients of the importance of hemoglobin testing

Decreases in sperm count

Fluid retention

EXHIBIT B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-290

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-290

NOV 20 2001

Actelion, Ltd.
Attention: Peter Hermann, Ph.D.
Gewerbestrasse 16
Allschwill
Ch-4123 Switzerland

Dear Dr. Hermann:

Please refer to your new drug application (NDA) dated November 17, 2000, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tracleer (bosentan) 62.5 and 125 mg Tablets.

We acknowledge receipt of your submissions dated September 11 and 25, October 4 and 15 and November 2, 8 and 19, 2001. Your submission of November 2, 2001 constituted a complete response to our September 17, 2001 action letter.

This new drug application provides for the use of Tracleer (bosentan) 62.5 and 125 mg Tablets for the treatment of pulmonary arterial hypertension.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Tracleer (bosentan) 62.5 and 125 mg Tablets under the regulations for accelerated approval for use as recommended in the final printed labeling (package insert), Medication Guide and carton and container labels included in your November 2, 2001 submission. Accordingly, the application is approved under 21 CFR 314 subpart H (314.500 – 560). Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations (21CFR 314.520) and the specific restrictions on distribution described below.

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. It is possible to consider different terms with the FDA at a later date.

Medication Guide

Pursuant to 21 CFR Part 208, FDA is notifying Actelion, Ltd. (hereinafter "Sponsor") that, based on information from pre-marketing studies, FDA has determined that Tracleer (bosentan) poses a serious and significant public health concern requiring distribution of the above-mentioned Medication Guide. Distribution of a Medication Guide is necessary for patients' safe and effective use of Tracleer. FDA has determined that Tracleer is a product for which patient labeling could help prevent serious adverse

effects. See 21 CFR Part 208.1(c). The Medication Guide for Tracleer must address the concerns about liver toxicity and pregnancy and the actions patients should take to avoid these serious adverse effects.

In accordance with 21 CFR 208, Actelion is responsible for ensuring the following:

- That a Medication Guide for Tracleer is available for every patient who is dispensed a prescription for Tracleer.
- That the label of each container of Tracleer includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom Tracleer is dispensed.
- That the label of each container includes a statement about how the Medication Guide is provided.

Tracleer Access Program

We remind you that your Tracleer Access Program is an important part of the postmarketing risk management for Tracleer, and must include all of the following components:

(1) Complete registration of all patients receiving Tracleer.
(2) Complete registration of practitioners who prescribe Tracleer.
(3) Distribution of Tracleer through a restricted distribution network.
(4) Distribution of the Tracleer Medication Guide to patients with each shipment of Tracleer.
(5) Initial distribution of Tracleer is to occur only after receipt by the distributor network of a written certification by the practitioner for an individual patient, stating that:

- Tracleer is being prescribed for a medically appropriate use in the treatment of Pulmonary Arterial Hypertension, as described in the Tracleer full prescribing information.
- The physician has reviewed the liver and pregnancy warnings with the patient and has committed to undertaking the appropriate monitoring of liver function tests and testing for pregnancy (if the patient is a female of child-bearing potential).

(6) An ongoing, comprehensive program to track and report to the FDA all fetal exposures to Tracleer and the outcomes of such exposures.
(7) An ongoing, comprehensive program to track and report to the FDA all adverse events related to liver injury in patients who receive Tracleer and the outcomes of those events (see below).
(8) An ongoing, comprehensive notification program that would respond to the collection of information from patients about their receipt of liver function testing and pregnancy testing in the previous month by providing (and recording) prompt feedback to the prescribing physicians about patients who are not compliant with this monitoring, or who are uncertain about their compliance with the monitoring. Such feedback must remind the physicians of the need for such ongoing monitoring.
(9) Review and assessment by the Sponsor and the FDA, at least on an annual basis, of the effectiveness of the Tracleer Access Program.

The Tracleer Access Program, as described in the attached documents, adequately addresses each of these requirements. Any changes to the program must be discussed with the FDA prior to their institution and are subject to FDA approval. We expect your continued cooperation to resolve any problems regarding the Tracleer Access Program that may be identified following Tracleer approval.

At the end of one year, and then annually, the Sponsor needs to provide the FDA with a detailed summary and analyses of the data available on all patients treated with Tracleer through the Tracleer Access Program, as a means of assessing the success of the program in minimizing patient pregnancy and liver toxicity. This summary should include the following:

- Summary demographic data on the use of Tracleer, both cumulative (from initial marketing) and during the previous year.
- Summary data on liver function monitoring and monitoring for pregnancy in patients taking Tracleer. This should include data on:
  - all feedback provided to the specialty distributors by the patients about their compliance with monthly liver function and pregnancy monitoring.
  - all feedback provided to the physicians by the specialty distributors about patient compliance with monthly liver function and pregnancy monitoring.
- Summary data on all reported clinical and laboratory adverse events related to the liver and any pregnancies.
- All materials submitted as part of the 15-day safety reports (see below).

We remind you of your specific reporting obligations regarding hepatotoxicity and pregnancies in patients who have received or are receiving Tracleer. In addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80), we ask that you initiate a 15-day safety report for:

- Any pregnancy.
- Any elevation in liver enzymes (aminotransferases) to > 8 times the upper limits of normal.
- Any elevations of liver enzymes (aminotransferases) accompanied by an elevation of bilirubin to ≥ 2 times upper limits of normal.
- Any clinical liver injury associated with hospitalization, liver transplant or death.

Postmarketing Studies (Phase 4 Commitments)

We remind you of your postmarketing study commitments, which are listed below.

(1) Investigation of the potential testicular toxicity of Tracleer in humans. Please submit a detailed proposal for a Phase 4 study or studies to examine the clinical effects of chronic treatment with Tracleer. Data to be collected as part of this commitment include:

- Semen analysis: total sperm count, semen volume, sperm concentration, sperm morphology and sperm motility. Analyses will need to be conducted at baseline followed by analyses through at least 6 months of drug exposure. If injury is detected, a follow-up analysis at least 3 months off drug will be important to assess reversibility.
- Assessment of the neurohormonal axis regulating male fertility: follicle stimulating hormone, inhibin, luteinizing hormone and total testosterone. Analyses will need to be conducted at baseline followed by analyses through at least 6 months of drug exposure.

(2) Investigation of potential metabolic interactions between Tracleer and hormonal contraceptives (*e.g.*, oral and implantable contraceptives). The goals of these investigations are to determine whether the use of Tracleer reduces the levels of these hormones in women through its induction of hepatic enzyme CYP 3A4 and whether the concomitant use of Tracleer decreases the effectiveness of these contraceptives in preventing ovulation. In order to characterize this effect of Tracleer adequately in humans, we ask that you submit a detailed proposal for a Phase 4 study or studies to examine the following effects of acute and chronic co-administration of Tracleer and

hormone-based contraceptives on the following parameters:

- Reproductive hormone levels in ovulating females.
- Ovulation.

Submit clinical and nonclinical protocol(s) to your IND for Tracleer and all study final reports to this NDA. In addition, under 21CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you are required to include a status summary of each commitment in your annual reports to this NDA. The status summary needs to include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report"**, or **"Postmarketing Study Correspondence."**

Chemistry and Manufacturing Issue

A dissolution specification of not less than [redacted]% (Q) dissolved in 30 minutes in 1% sodium lauryl sulfate in water at a paddle speed of 50 rpm is recommended. Data related to this goal should be submitted to the FDA as they become available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21CFR 314.80 and 314.81.

If you have any questions, please call:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc:
Actelion Ltd.
Attention: Thomas W. Lategan, D.Phil.
56 Huckleberry Lane
North Andover, MA 01845

Tracleer™ Access Program (TAP)

The purpose of this document is to describe the plans for a restricted distribution network for Tracleer (Tracleer Access Program or TAP) and development of a patient database to follow patients treated with Tracleer. This plan was outlined to the FDA's Cardiovascular and Renal Drugs Advisory Committee on August 10, 2001. TAP will provide a mechanism to assist with 2 primary risk management goals for Tracleer therapy.

1. Pregnancy prevention
2. Liver enzyme monitoring and prevention of hepatic injury

Actelion is absolutely committed to a comprehensive physician and patient education campaign that will highlight these two goals.

How the TAP system works:

1. A toll free line provides physicians with initial information about Tracleer, a site to report adverse events, and provides customer service. The toll free line offers 3 choices:

   A. Press 1 - Tracleer Access Program provides initial information and contact information including fax number and patient enrollment form if needed. TAP creates and maintains a central database. TAP triages the prescription to a Specialty Distributor (SD).
   B. Press 2 – The Medical Information and Drug Safety Reporting Line. The physician or patient may ask questions, request information or report adverse events (AEs). In the event of an AE related to liver function test (LFT) elevations or pregnancy, a form is completed and faxed to Actelion for review and follow-up. This line is also the contact point with physicians if the medication is discontinued or not refilled.
   C. Press 3 – Customer Service. For all other issues.

2. Following the toll-free call, a completed Patient Enrollment Form is faxed to TAP to initiate the prescription. The form serves as the prescription, allowing a one month supply (with refills) of drug, providing patient information and including important physician certifications.

3. Each Specialty Distributor (SD) must agree to a defined set of rules to sell Tracleer. The rules include, but may not be limited to:

   A. Inserting two patient reminders in the monthly prescription:
      a. The approved Patient Medication Guide
      b. A LFT and Pregnancy testing reminder card

      Note: These will remind the patient to have LFTs checked. Females of child-bearing potential are also reminded of the importance of testing for pregnancy monthly, and preventing pregnancy using appropriate birth control methods. Patients are also reminded to contact their physician if they experience adverse events or have questions.

The SD must make a database entry verifying completion of this contact.

B. Generating a letter to the prescribing physician in which the SD indicates that the initial prescription for Tracleer has been filled (date) for the patient (name). The letter will contain the name of the SD along with a contact number for the physician to call if there is any need to alter the dosage of Tracleer. This letter will also remind the doctor to check the LFT s monthly and that female patients should not become pregnant or take Tracleer during pregnancy and should have pregnancy testing done monthly. Finally, the physician will be reminded to report any relevant AE's to the Actelion Drug Safety Reporting Line (1-866-228-3546) and/or the Food and Drug Administration (1-800-FDA-1088)

C. Calling the patient prior to the scheduled shipment of the next months medication and asking them if they are continuing on Tracleer. If they are, they should be reminded of the need for liver function tests and asked if they have had a blood draw in the last month for reasons other than checking blood thinning. If a patient is female of child-bearing potential, she should be asked if she has had a pregnancy test within the last month and be reminded that she should not become pregnant while on Tracleer.

D. If the patient has not had a liver or pregnancy test within the last month, or is unsure, then the SD will communicate this promptly to the physician and remind the physician of the need for liver and/or pregnancy monitoring. The initial call to the patient and the contact with the physician will be logged.

E. If a planned refill doesn't occur, the TAP Administrator will determine why. If the reason is medical, the physician will be contacted to determine what the medical issue is, and whether the issue is related to LFT elevation or change in pregnancy status. That information will be entered into the TAP database. Adverse events will be forwarded to the Actelion Director of Drug Safety for follow up and reporting.

4. The Patient Enrollment Form contains a statement : "I certify that I am prescribing Tracleer™ (bosentan) for this patient for a medically appropriate use in the treatment of Pulmonary Arterial Hypertension, as described in the Tracleer™ full prescribing information. I have reviewed the liver and pregnancy warnings with the patient and commit to undertaking appropriate blood testing for monitoring liver function in this patient and testing for pregnancy (if the patient is a female of child-bearing potential)." This statement is followed by a place for the physician's signature.

Tracleer™ (bosentan) Patient Enrollment

Phone 1-866-228-3546 or Fax 1-866-279-0669

PO Box 220829 Charlotte, North Carolina 28222-0829

Upon receipt of this patient enrollment form to the Tracleer Access Program (TAP), a representative will verify the patient's benefits to determine coverage, assign a specialty distributor based on benefits, and coordinate with this distributor to facilitate access to Tracleer. The specialty distributor will follow up as needed with the prescriber and will ensure appropriate distribution of the drug.

Please Select: ☐ **Newly Prescribed Patient** ☐ **Patient Currently on Tracleer** ☐ **Clinical Trial Patient**

PATIENT INFORMATION (Please print)

Name: _____ SSN#: _____ DOB: _____

Address: _____ City: _____ State: _____ Zip: _____

Phone Numbers Day: ___ - ___ - _____ Evening: ___ - ___ - _____ Sex: ☐ M ☐ F

INSURANCE INFORMATION (Include copies of insurance cards if possible)

Primary Insurance Co. Name: _____ Phone #: ___ - ___ - _____

Policy Holder Name: _____

Policy #: _____ Group #: _____

Prescription Card Name: _____ Phone #: ___ - ___ - _____

Policy #: _____ Group #: _____

Secondary Insurance Co. Name: _____ Phone #: ___ - ___ - _____

Policy Holder Name: _____ Policy #: _____ Group #: _____

I authorize The TRACLEER™ ACCESS PROGRAM and its distributors to obtain and disclose information to my insurance company, government agency or other parties, on my behalf, as necessary to obtain reimbursement approval for Tracleer™ (bosentan). My name and street address information shall not be divulged to ACTELION or any other party unless necessary to comply with laws, regulations or other requirements necessary to deal with safety, adverse event and related issues.

Patient/Guardian Signature: _____ **Date:** _____

PHYSICIAN INFORMATION

Prescriber Name & Title: _____ DEA#: _____

Name of Facility: _____ State License #: _____

Contact Name: _____ Physician Specialty: _____

Address: _____

City: _____ Physician e-mail: _____

State: _____ Zip: _____

Phone: ___ - ___ - _____ Fax: ___ - ___ - _____

PRESCRIPTION

☐ Tracleer 62.5 mg
(66215-0101-06)
Refills # _____

☐ Tracleer 125 mg
(66215-0102-06)
Refill # _____

Instructions: _____

Ship to: ☐ Physician Office ☐ Patient's home ☐ Other(specify): _____

Address (no P.O. Box): _____

City, State, Zip: _____

Ship Attn: _____

STATEMENT OF MEDICAL NECESSITY

Diagnosis: ☐ Pulmonary Arterial Hypertension (ICD _____)

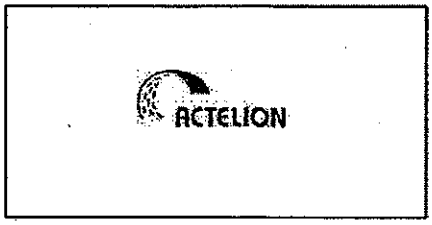
Related To: ☐ Primary Pulmonary Hypertension (ICD 416.0) ☐ Scleroderma (ICD 710.1) ☐ Lupus (ICD 710.0)
☐ HIV (ICD _____) ☐ Congenital Heart (ICD _____) ☐ Other (ICD _____)

I certify that I am prescribing Tracleer™ (bosentan) for this patient for a medically appropriate use in the treatment of Pulmonary Arterial Hypertension, as described in the Tracleer™ full prescribing information. I have reviewed the liver and pregnancy warnings with the patient and commit to undertaking appropriate blood testing for monitoring liver function in this patient and testing for pregnancy (if the patient is a female of child-bearing potential).

Prescriber's Signature: **Date:**

Internal Use Only: **Date to TAP:** _____ **Patient ID:** _____
(REV16111901F1) **Assigned Distributor:** _____

EXHIBIT C



NEW SUPPLEMENT FOR NDA 21-290

Tracleer (bosentan)
Actelion Clinical Research, Inc.
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Risk Evaluation Mitigation Strategy (REMS)
REMS MODIFICATION

January 31, 2010

Document No: D-10.076

I. GOAL(S)

The goals of the Tracleer risk evaluation and mitigation strategy are as follows:

1. To enable informed risk-benefit decisions for treating patients with Tracleer.
2. To minimize the risk of hepatotoxicity in patients who are exposed to Tracleer.
3. To minimize the risk of fetal exposures in female patients who are exposed to Tracleer.
4. To educate prescribers, patients, and pharmacies on the safe-use conditions for Tracleer.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each 30-day supply of Tracleer and in accordance with 21 CFR 208.24.

B. Elements to Assure Safe Use

1. Tracleer will only be prescribed by healthcare professionals who are certified by Actelion under 505-1(f)(3)(A)
    a. Actelion will ensure that physicians and other appropriately licensed healthcare providers who prescribe Tracleer are specially certified. Actelion will ensure that each prescriber agrees, on the Prescriber Certification section of the Tracleer Enrollment and Renewal Form each time he or she prescribes Tracleer, that he or she has read and understood the Tracleer Prescriber Essentials training guide and documented that he or she:
        i. Has enrolled patients in the REMS program (the Tracleer Access Program [T.A.P]), and documented each enrollment.
        ii. Has reviewed and discussed the Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with their patients prior to prescribing Tracleer
        iii. Has reviewed pretreatment liver function tests and confirmed that Female patients of Child Bearing Potential (FCBP) are not pregnant
        iv. Has ordered and will monitor monthly liver tests and for FCBP, pregnancy tests
        v. Has educated and counseled any FCBP to notify the prescriber if she suspects she might be pregnant

vi. Has educated and counseled any FCBP about the need to use reliable methods of contraception during treatment with Tracleer and for one month after treatment discontinuation
vii. Will notify Actelion of any adverse events, including hepatotoxicity, and to report any pregnancy during treatment with Tracleer
viii. Will counsel patients who fail to comply with program requirements
ix. For patients continuing therapy, will re-enroll patients into the REMS program after the first 12 months of treatment then annually thereafter

b. Actelion will

i. Ensure that prescribers' enrollment information and date of certification is linked to their enrolled patients' information in a validated (T.A.P.) database

ii. Ensure that the patient information from a new prescriber is linked in the T.A.P. database with information from the prior prescriber

iii. Any prescribers who have had fewer than six patients on bosentan will be retrained at 6 months following the initial patient enrollment and training. A copy of the Essentials kit and a reminder letter will be sent to these prescribers to remind them of the risks of Tracleer and the need for ongoing monitoring to assure safe use of Tracleer

iv. Maintain a database of certified prescribers in the REMS program. Actelion will monitor prescribers' certification requirements and prescription data and may de-enroll noncompliant prescribers until the requirements are met

v. Create a new reporting database that will link adverse events of interest extracted from the Drug Safety Database (Argus Safety™) with relevant information, such as enrolled patients, certified prescribers and pharmacies.

vi. Generate a report each month from the T.A.P. database to identify any prescription that exceeds a 30-day supply.

c. The following materials are part of the REMS and are appended:

i. Tracleer Enrollment and Renewal Form

ii. Prescriber Essentials guide

iii. Prescriber letter

2. Tracleer will only be dispensed by pharmacies, practitioners, and health care settings (dispensers) that are specially certified by Actelion under 505-1(f)(3)(B).

a. Actelion will ensure that Tracleer dispensers are specially certified. Tracleer will only be dispensed by pharmacies that are specially certified. Actelion will ensure that, to be certified, they are under legal contract and that they will:

i. Receive and accept prescriber and patient enrollment forms only from PAH Pathways, the entity that administers TAP.

ii. Counsel patients

1. on the risks of Tracleer, including the risks of liver injury and serious birth defects

2. on the need to complete a monthly liver function test and pregnancy test (for FCBP as defined on the Tracleer Enrollment and Renewal Form)

iii. Counsel all FCBP on the need to use reliable contraception (as defined in the Tracleer Enrollment and Renewal Form) during Tracleer treatment and for one month after treatment discontinuation, and the need to inform their prescriber if they suspect they may be pregnant

iv. For product that will be dispensed and shipped to the patient, confirm the drug shipment address with the patient

v. Dispense Tracleer only as 30-day supplies (except as described below) and require monthly refills

vi. Dispense Tracleer only to patients enrolled in the REMS program

vii. Provide a Medication Guide to patients each time Tracleer is dispensed

viii. Speak with each patient, or their prescriber, every month to obtain confirmation that liver function testing and pregnancy testing was completed.

ix. Dispense a 30-day supply of Tracleer (for patients not traveling outside the United States for more than 30 days) only upon completing the following process:

1. Obtain confirmation from the patient that the testing was completed.

2. If unable to obtain confirmation from the patient that the testing was completed, or if the patient cannot be reached, obtain confirmation from the patient's prescriber.

3. If the patient's prescriber cannot confirm that the required testing was completed, the certified pharmacy will:

a. Remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for FCBP)

b. Ask the prescriber whether or not he/she authorizes the refill of Tracleer. The patient is eligible to receive a 30-day supply of Tracleer only if the prescriber authorizes the refill of Tracleer.

x. For patients traveling outside the United States for more than 30 days, the following process must be completed:

1. The certified pharmacy is notified by an enrolled patient and/or certified prescriber of the need to fulfill a greater than 30-day supply due to the patient's extended travel outside the US.
2. The certified pharmacy contacts the patient and the prescriber to verify the need. The certified pharmacy explains the process to the patient, and tells them that the form (FRM-549-COP-US) will be sent to the certified prescriber for completion and submission.
3. The certified pharmacy provides the prescriber with a letter explaining the process, and the request form (FRM-549-COP-US).
4. The certified prescriber completes the form and faxes it to the certified pharmacy.
5. The certified pharmacy reviews the form for completeness and contacts either the certified prescriber or the patient to obtain any additional information.
6. The medication is shipped to the patient, along with the Medication Guide and the required patient information sheet.
7. The certified pharmacy documents in their data management system that the patient met the criteria for the greater than 30-day supply due to foreign travel. This information is sent to Actelion as usual with the dispensed amount (in tablets), dose, and frequency captured.
8. The certified pharmacy contacts the prescriber for the monthly call in this situation to determine if safe-use conditions are being followed by the patient and prescriber. This is documented in the certified pharmacy data management system.

xi. Call patients, who discontinue Tracleer treatment, or their prescriber, to determine the reason for treatment discontinuation and record this information for inclusion in the T.A.P. validated database

xii. Notify Actelion of any reports of adverse events, including liver injury, and any reports of pregnancy.

xiii. Agree to collect and report to Actelion specific data requirements needed to ensure compliance with the Tracleer REMS program including shipment records for every time Tracleer is dispensed. Actelion maintains the data in the T.A.P. database.

b. Actelion will ensure that a designated representative of each certified pharmacy:

i. is trained on the REMS program.

ii. trains pharmacy staff on the REMS program procedures and REMS materials prior to dispensing Tracleer

iii. agrees that the certified pharmacy may be audited by the FDA, Actelion, or a third party designated by Actelion

c. The following materials are part of the REMS and are appended:

i. FRM 549-COP-US, Request for > 30-Day Supply.

ii. Prescriber letter from certified pharmacy (accompanies FRM-549-COP-US)

iii. Patient Information Sheet (to be provided to the patient by the certified pharmacy)

3. Tracleer will only be dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D):

a. Actelion will ensure that patients treated with Tracleer are enrolled in the REMS program and assigned a unique identifying number before Tracleer is dispensed to him or her. Actelion will ensure that to become enrolled each patient consents to participate in the program for as long as they are taking the medication by acknowledging that he or she:

i. has read the Tracleer Medication Guide and patient educational materials and

ii. agrees to be contacted, prior to each shipment of Tracleer, to obtain confirmation that liver function testing and, if applicable, pregnancy testing was completed and

iii. agrees to be counseled on the requirements of the REMS program and the risks of Tracleer.

iv. acknowledges, in the case of a FCBP, that she will be contacted to respond to a pregnancy questionnaire if she becomes pregnant while on Tracleer.

b. Actelion will ensure that, to continue receiving Tracleer, each patient is re-enrolled every 12 months following their initial enrollment.

c. The following materials are part of the REMS and are appended:

i. Patient Essentials Guide

C. Implementation System

The Implementation System includes the following:

1. Actelion will maintain a database capturing certified prescribers, pharmacies and patients. Actelion will create a new reporting database that will link adverse events

of interest extracted from the Drug Safety database (Argus Safety™) with relevant information, such as enrolled patients, certified prescribers and pharmacies.

2. Actelion will monitor distribution and prescription data to ensure that only certified pharmacies are distributing and dispensing Tracleer. The certified pharmacies are the only distributors of Tracleer. Therefore, the distribution data will be the same as the prescription data.

3. Actelion will audit all certified pharmacies against their formal procedures and contractual arrangements at least once every 12 months and more frequently if non-compliance issues are identified.

4. Actelion will ensure that the pharmacies follow an agreed upon, scripted process to follow when a patient is identified as non-compliant with the testing, or the compliance with the required testing is uncertain in the previous month. The scripted process includes steps whereby the pharmacy provides prompt feedback to the prescriber on the potential non-compliance circumstances and reminds the prescriber of the need for ongoing monitoring. The pharmacies record their actions, and notify T.A.P.

5. Actelion will collect information from the pharmacies about compliance with hepatic and pregnancy testing and monitor the data in the T.A.P. database.

D. Timetable for Submission of Assessments

Actelion will submit REMS assessments to FDA annually on January 19th. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Actelion will submit each assessment so that it will be received by the FDA on or before the due date.

Tracleer® (bosentan) Enrollment and Renewal

Check one: ☐ **Enrollment** ☐ **Renewal**

PO Box 826, South San Francisco, CA 94083-0826 | Phone 1-866-ACTELION (1-866-228-3546) or Fax 1-866-279-0669

Once complete, submit this form to PAH Pathways.™ The information will be entered into the Tracleer Access Program (T.A.P.®) database and forwarded to the specialty pharmacy you designate below. The specialty pharmacy will follow up as needed with prescribers and patients.

Patient Information

First name:	MI:	Last name:		Gender: ☐ Male ☐ Female
SSN:		DOB:	Phone #:	
Address:		City:	State:	ZIP:
Legal guardian/emergency contact:		Relationship:	Phone #:	
Shipping directions: ☐ Physician office ☐ Patient's home ☐ Hospital		Shipping attn:		
Shipping address:		City:	State:	ZIP:

Diagnosis: Pulmonary arterial hypertension (check subtypes): ☐ Familial ☐ Idiopathic ☐ Scleroderma ☐ HIV ☐ Lupus ☐ Portal hypertension ☐ Congenital heart defects ☐ Pulmonary hypertension—other etiologies: _____ ☐ Other: _____

Required: Please submit copies of patient's current medical and prescription cards with this form.

Insurance Information

Primary insurance company:			Phone #:
Name of insured:		Policy #:	Group/Policy #:
Prescription coverage name:	Phone #:	Policy #:	Group/Policy #:
Indicate specialty pharmacy preference:			

For a current list of pharmacies, call 1-866-228-3546. If no preference is indicated, this referral will be sent to the appropriate specialty pharmacy based on the patient's existing benefits.

I have read and agreed to the Patient Agreement on the back of this form. I have reviewed the Medication Guide with my prescriber, I consent to be enrolled in the Tracleer Access Program, and I agree to comply with the program for as long as I am prescribed Tracleer.

Patient Signature

Prescriber and Prescription Information

First name:	MI:	Last name:		Degree:
DEA #:		NPI:		

Complete section below only if you are a new prescriber or your contact information has changed.

Name of facility:		Specialty:	Tax ID #:	State license #:
Office contact (name and phone):		Phone #:		Fax #:
Primary address:	City:	State:	ZIP:	E-mail:

For the patient indicated on this form, please indicate whether:

1. You have reviewed pretreatment liver function tests. ☐ Yes ☐ No
2. If a female, she is of childbearing potential. ☐ Yes ☐ No
3. If a female of childbearing potential, you have confirmed a pretreatment negative pregnancy test. ☐ Yes ☐ No

☐ Tracleer 62.5 mg (66215-0101-06) Refills #: _____

☐ Tracleer 125 mg (66215-0102-06) Refills #: _____ Dispense as Written

Directions for use:

Prescriber Certification—My signature below certifies that:

1. I have read and understood the communication and educational materials for prescribers regarding the risks of Tracleer, and agree to document that I:
   - –Reviewed and discussed the Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with my patients prior to prescribing Tracleer.
   - –Reviewed pretreatment liver function tests (ALT/AST/bilirubin) and confirmed that my patients are not pregnant (if applicable), and I agree to order and monitor monthly liver function tests and, if applicable, pregnancy tests.
   - –Educated and counseled females of childbearing potential **(see definition on reverse side)** to notify me if they suspect they may be pregnant.
   - –Educated and counseled females of childbearing potential about the need to use reliable methods of contraception **(see table on reverse side)** during treatment with Tracleer and for one month after treatment discontinuation.
2. I will notify Actelion Pharmaceuticals US, Inc., and/or the FDA, of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer.
3. I will counsel my patients who fail to comply with the program requirements.
4. I will renew my patients' prescriptions annually by completing and submitting a new form for patients continuing therapy.

Prescriber Signature Date

Prescriber Signature Date

BEFORE SIGNING, SEE IMPORTANT SAFETY INFORMATION ON BACK.

 8361138 0809

Tracleer (bosentan) Enrollment and Renewal

PO Box 826, South San Francisco, CA 94083-0826
Phone 1-866-ACTELION (1-866-228-3546) or Fax 1-866-279-0669

Patient Agreement

- I have reviewed the Medication Guide with my healthcare provider. I understand that a Medication Guide will be provided to me each time I receive a prescription for Tracleer, and that I must read it each time because it may have new information important to my treatment.
- I have been informed of the risks of treatment with Tracleer, including the risks of liver injury and birth defects. I understand that I will be contacted by Actelion, its agents, and/or a healthcare provider to receive counseling on the risks of Tracleer treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for females of childbearing potential—see definition below) and, if I am a female who becomes pregnant, to obtain information about my pregnancy.
- I agree to notify Actelion or my specialty pharmacy if I should change prescribers.
- I agree to have monthly blood tests as ordered by my healthcare provider for as long as I take Tracleer.
- I authorize my healthcare providers, health plans, other payers, and pharmacies to disclose my personal, medical, and health information to Actelion Pharmaceuticals US, Inc., and its employees, distributors, agents, and contractors ("Actelion"), and I authorize Actelion to use and disclose this information for use in implementing T.A.P. including to 1) establish my benefit eligibility; 2) communicate with my healthcare providers, health plans, other payers, and pharmacies about my medical care; 3) provide support services, including facilitating the provision of Tracleer to me; and 4) help find ways to pay for Tracleer, or for treatment or healthcare operations in progress.
- I understand that I may be contacted by Actelion or its delegates regarding important safety surveys while I am taking Tracleer.
- I understand that Actelion does not promise to find ways to pay for my Tracleer, and I know that I am responsible for the costs of my care.
- I understand that once my health information has been disclosed to Actelion, privacy laws may no longer restrict its use or disclosure; however, Actelion agrees to protect my information by using and disclosing it only for the purposes described above or as required by law.
- I acknowledge and agree that, although Actelion will have access to my personal health information, Actelion will not be providing counseling or medical advice regarding my condition. I further understand that all questions regarding my medical and health conditions should be discussed with my healthcare provider.

Definition of Female of Childbearing Potential (FCBP)

Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).

Reliable methods of contraception during treatment with Tracleer

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Transdermal patch —Vaginal ring • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

PRESCRIBER ESSENTIALS

Your guide to enrolling and renewing patients in the Tracleer Access Program (T.A.P.)

Please see accompanying full prescribing information.

PAHPathways™
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

Tracleer
BOSENTAN TABLETS

Introduction to the essentials

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) in patients with WHO Class II-IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these potential benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses. Prescribers of Tracleer must be aware of risks associated with treatment, including the risks of hepatotoxicity and teratogenicity.

Before you prescribe Tracleer, you must familiarize yourself with the content of this educational guide, as well as the full prescribing information in the back pocket. To receive Tracleer, patients must be enrolled in the Tracleer Access Program (T.A.P.®), which is done by completing and submitting the Tracleer Enrollment and Renewal form. With each prescription (both initial enrollments and annual renewals), you must certify that you are aware of and have fulfilled essential steps that will help ensure the ongoing safe use of Tracleer. Prescriber Certification is part of the Tracleer Enrollment and Renewal form.

As a certified prescriber of Tracleer, you may be contacted periodically to provide feedback regarding the effectiveness of T.A.P. to further ensure the ongoing safe use of Tracleer.

Service and support essentials

Tracleer Access Program (T.A.P.)

Because of the risks associated with treatment, the use of Tracleer requires participation in the Tracleer Access Program (T.A.P.), a restricted distribution program. In order to receive Tracleer, prescribers and patients must enroll in T.A.P. and agree to comply with the requirements of this program. Enrollment in T.A.P. is accomplished by completing and submitting the Tracleer Enrollment and Renewal form. T.A.P. is administered by PAH Pathways. You can reach PAH Pathways by calling toll-free at 1-866-ACTELION (1-866-228-3546).

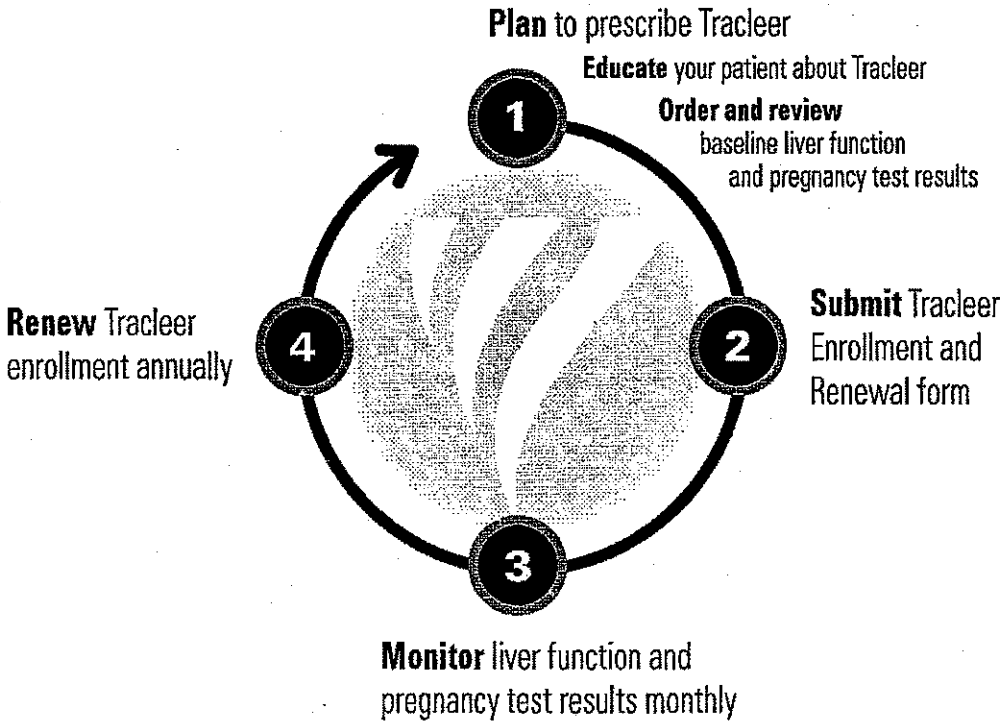
Certified specialty pharmacies

Tracleer is not dispensed through retail pharmacies; rather, Tracleer is dispensed through a restricted network of certified specialty pharmacies. Specialty pharmacies help with patient management by confirming required monthly liver function and pregnancy testing. Specialty pharmacies also arrange for Tracleer to be delivered conveniently and directly to patients each month. If a patient does not confirm having the monthly tests or becomes pregnant, the pharmacy will contact you.

Please see accompanying full prescribing information.

For patients with pulmonary arterial hypertension (PAH) WHO Class II-IV

4 ESSENTIAL steps to enrollment and renewal



1 Plan to prescribe Tracleer

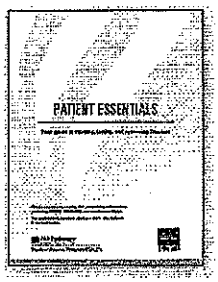
Tracleer is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class II-IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these potential benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

You must address and document (see step 2) these points with every Tracleer enrollment or renewal:

- Before prescribing Tracleer, review the Medication Guide and discuss the risks of treatment with your patients, including the risks of hepatotoxicity and teratogenicity.
- Order and review pretreatment liver function tests (ALT/AST/bilirubin) and confirm that your female patients of childbearing potential are not pregnant. **See the definition of "Female of childbearing potential" on page 9.**
- Agree to order and monitor monthly liver function and, if applicable, pregnancy tests.
- Educate and counsel females of childbearing potential on the need to use reliable methods of contraception during treatment with Tracleer and for 1 month after treatment discontinuation. See the table "Reliable methods of contraception" on page 9.
- Educate and counsel females of childbearing potential to notify you if they suspect they may be pregnant.

You must also agree to:

- Counsel any patient who fails to comply with the program requirements
- Notify Actelion Pharmaceuticals US, Inc., and/or the FDA, of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer
- Renew your patients' Tracleer enrollment annually by completing and submitting a new Tracleer Enrollment and Renewal form



The Patient Essentials guide is available to help you discuss the steps of Tracleer enrollment and renewal with your patients. The Tracleer Medication Guide, which you must review with your patients prior to prescribing Tracleer, is included in its entirety in the Patient Essentials guide and also in its back pocket.

Please see accompanying full prescribing information.

For patients with pulmonary arterial hypertension (PAH) WHO Class II-IV

2 Submit Tracleer Enrollment and Renewal form

Tracleer® (bosentan) Enrollment and Renewal

Check one: ☐ Enrollment ☐ Renewal

PO Box 826, South San Francisco, CA 94083-0826 | Phone 1-866-ACTELION (1-866-228-3546) or Fax 1-866-279-0669

Once complete, submit this form to PAH Pathways.® The information will be entered into the Tracleer Access Program® database and forwarded to the specialty pharmacy you designate below. The specialty pharmacy will follow up as needed with prescribers and patients.

you must:

- Read and complete it in its entirety
- Sign the Prescriber Certification
- Complete and sign the prescription information
- Document patient consent to the terms of the Tracleer Enrollment and Renewal form
- Fax the form to 1-866-279-0669
- Keep copies of all completed Tracleer Enrollment and Renewal forms.

Patient Information

First name: MI: Last name: Gender: ☐ Male ☐ Female

Legal guardian/emergency contact: Relationship: Phone #:

Shipping directions: ☐ Home ☐ Office ☐ Pharmacy ☐ Hospital Shipping attn: Degree:

Shipping address: City:

Etiology: ☐ Pulmonary arterial hypertension (check subtype(s)): ☐ Familial ☐ Idiopathic ☐ Scleroderma ☐ HIV ☐ Lupus ☐ Portal hypertension ☐ Congenital heart defects ☐ Pulmonary hypertension—other etiologies: ☐ Other:

Required: Please submit copies of patient's current medical and prescription cards with this form.

Insurance Information

Primary insurance company: Phone #:

Name of insured: City: State: ZIP: Country: Policy #: Group/Policy #:

Prescriber Certification—My signature below certifies that:

1. I have read and understood the communication and educational materials for prescribers regarding the risks of Tracleer, and agree to document that I:
   - –Reviewed and discussed the Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with my patients prior to prescribing Tracleer.
   - –Reviewed pretreatment liver function tests (ALT/AST/bilirubin) and confirmed that my patients are not pregnant (if applicable), and I agree to order and monitor monthly liver function tests and, if applicable, pregnancy tests.
   - –Educated and counseled females of childbearing potential (see definition on reverse side) to notify me if they suspect they may be pregnant.
   - –Educated and counseled females of childbearing potential about the need to use reliable methods of contraception (see table on reverse side) during treatment with Tracleer and for one month after treatment discontinuation.
2. I will notify Actelion Pharmaceuticals US, Inc., and/or the FDA, of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer.
3. I will counsel my patients who fail to comply with the program requirements.
4. I will renew my patients' prescriptions annually by completing and submitting a new form for patients continuing therapy.

Prescriber Information

Prescriber name: Degree:

Office contact (name and phone): Fax #:

Practice address: City: State: ZIP: E-mail:

Tax ID #: DEA #: State license #:

Prescriber signature: John Doe MD Date:

Prescriber and Prescription Information

For the patient indicated on this form, please indicate whether:

1. You have reviewed pretreatment liver function tests. ☐ Yes ☐ No
2. If a female, she is of childbearing potential. ☐ Yes ☐ No
3. If a female of childbearing potential, you have confirmed a pretreatment negative pregnancy test. ☐ Yes ☐ No

☐ Tracleer 62.5 mg (66215-0101-06) Refills #: _____

☐ Tracleer 125 mg (66215-0102-06) Refills #: _____ Dispense as Written

Directions for use:

John Doe MD

Prescription Information

BEFORE SIGNING, SEE IMPORTANT SAFETY INFORMATION ON BACK.

Tracleer® BOSENTAN TABLETS

3 Monitor liver function and pregnancy test results monthly

Safe use of Tracleer requires that you obtain and review monthly liver function and, if applicable, pregnancy tests. You must counsel your patients about the importance of monthly testing and ensure that test results are obtained and reviewed by your office. The specialty pharmacy will confirm with your patients that monthly tests have been obtained. If a patient does not confirm having the monthly tests or becomes pregnant, the pharmacy will contact you. Notify Actelion and/or the FDA of any pregnancies or adverse events, including liver injury, by calling toll-free at 1-866-ACTELION (1-866-228-3546).

Elevated monthly liver function test results do not preclude treatment with Tracleer. The table below provides recommendations on managing Tracleer patients with elevated liver function test results.

Tracleer aminotransferase (ALT/AST) management[1]

ALT/AST level	Treatment and monitoring recommendations
≤3 × ULN*	**Continue** to monitor; no change in monitoring schedule or dosage
>3 to <5 × ULN	**Confirm** by another test; **if confirmed, reduce the dose or interrupt** treatment and monitor LFT levels every 2 weeks **Continue or reintroduce† Tracleer** if levels return to pretreatment levels
>5 to ≤8 × ULN	**Confirm** by another test; if confirmed, stop therapy; monitor LFTs at least every 2 weeks **Consider** reintroduction† of therapy if LFTs return to pretreatment levels
>8 × ULN	**Stop** therapy; do not reintroduce

*Upper limit of normal.

†If Tracleer is reintroduced it should be at the starting dose; aminotransferase levels should be checked within 3 days.

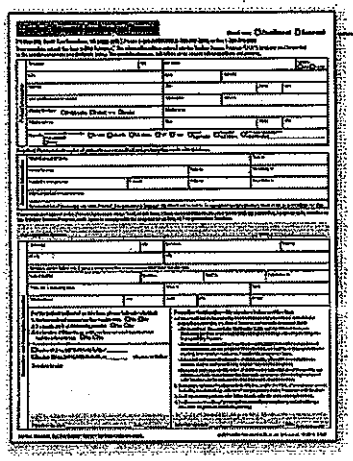
Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

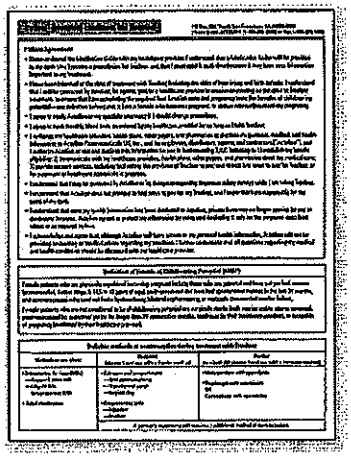
Please see accompanying full prescribing information.

For patients with pulmonary arterial hypertension (PAH) WHO Class II-IV

4 Renew Tracleer enrollment annually

In order to continue your patients on Tracleer, you must return to the start of the process (step 1) annually and review the educational materials about Tracleer benefits and risks with your patients. You must also complete steps 2 and 3, including obtaining patient consent and signing both prescriber signature sections of the Tracleer Enrollment and Renewal form. The form gives you a choice at the top of whether your patient is new to Tracleer (enrollment) or continuing on therapy (renewal). Check the renewal box, complete the form, and fax it to PAH Pathways™ at 1-866-279-0669. Keep a copy for your records.





Check one: ☐ Enrollment ☑ Renewal

Safety profile: Liver warnings

The following pages contain important safety information about treatment with Tracleer® (bosentan). You must be familiar with this information before prescribing Tracleer.

Tracleer may cause liver damage

- In the Tracleer pivotal clinical trials, Tracleer caused at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases.
- Because these changes are a marker for potential serious liver injury, liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter.
- Elevations in aminotransferases require close attention.
- Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Liver enzyme elevations: experience and management

- Use of Tracleer should generally be avoided in patients with elevated aminotransferases (>3 × ULN) **at baseline** because monitoring liver injury may be more difficult.
- It is important to adhere strictly to the monthly monitoring schedule for the duration of treatment.
  - Changes in aminotransferases may occur early or late in treatment.
  - There have been rare postmarketing reports of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring; the contribution of Tracleer could not be excluded.
- For treatment and monitoring recommendations, see the table on page 6.
  - For patients whose **monthly** LFTs are ≤3 × ULN, no change in monitoring schedule or dosage is required.
  - For patients whose **monthly** LFTs are >3 × ULN, close monitoring and either dose reduction or treatment cessation are necessary.

Please see accompanying full prescribing information.

Safety profile: Pregnancy warnings

Pregnancy must be excluded and prevented

- Tracleer is likely to cause major birth defects if used by pregnant females, based on animal data.
- To prevent pregnancy, females of childbearing potential must use reliable methods of contraception during treatment and for 1 month after stopping Tracleer.
- Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives, should not be used as the sole means of contraception because they may not be effective in patients receiving Tracleer.
- Monthly pregnancy tests should be obtained.
- Please remember that a patient receiving Tracleer can transition into a female of childbearing potential during the course of therapy.

Female of childbearing potential

- Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.
- Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).

Reliable methods of contraception during treatment with Tracleer

- Females of childbearing potential using Tracleer must use 2 reliable methods of contraception unless they have had a tubal sterilization or have a Copper T 380A IUD or LNg-20 IUS.

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Transdermal patch —Vaginal ring • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

Safety profile: Warnings, precautions, adverse events, and drug interactions

Safety profile when administered with other standard PAH medications in Study 351, BREATHE-1, and EARLY

- Patients receiving Tracleer continued other medications, including anticoagulants, digoxin, diuretics, and vasodilators such as calcium channel blockers and ACE inhibitors.[2,3]
- Patients receiving epoprostenol within 3 months of study screening were ineligible for participation.[2,3]

Fluid retention

- Peripheral edema is a known clinical consequence of PAH and worsening PAH, and is also a known effect of other endothelin receptor antagonists.
- In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7% (placebo-corrected) of patients.
- There have been postmarketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer.
- If clinically significant fluid retention develops, further evaluation should be undertaken to determine the cause, and the possible need for treatment or discontinuation of Tracleer therapy.

Effect on sperm count

- In an open-label study (N=25), a decline in sperm count of at least 50% in 25% of Tracleer-treated patients was observed after 3 or 6 months. Sperm count remained in normal range after 6 months, with no changes in sperm morphology, sperm motility, or hormone levels.
- It cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Associated with dose-related decreases in hemoglobin[1]

- Decreases in hemoglobin concentration:
  - Measured 0.9 g/dL (overall mean decrease) for Tracleer-treated patients
  - Were detected during the first few weeks of treatment
  - Stabilized by 4 to 12 weeks of treatment
- Monitoring of hemoglobin concentrations recommended after 1 and 3 months, and quarterly thereafter

Pulmonary veno-occlusive disease (PVOD)

- If signs of pulmonary edema occur when Tracleer is administered, the possibility of associated PVOD should be considered and Tracleer should be discontinued.

Please see accompanying full prescribing information for complete description of adverse events.

Adverse events

Adverse events occurring in ≥3% of patients treated with Tracleer and more frequently than the placebo group*[1]

Adverse Event	Tracleer (n=258)		Placebo (n=172)	
Respiratory tract infection	56	22%	30	17%
Headache	39	15%	25	14%
Edema	28	11%	16	9%
Chest pain	13	5%	8	5%
Syncope	12	5%	7	4%
Flushing	10	4%	5	3%
Hypotension	10	4%	3	2%
Sinusitis	9	4%	4	2%
Arthralgia	9	4%	3	2%
Liver function test abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	-	-

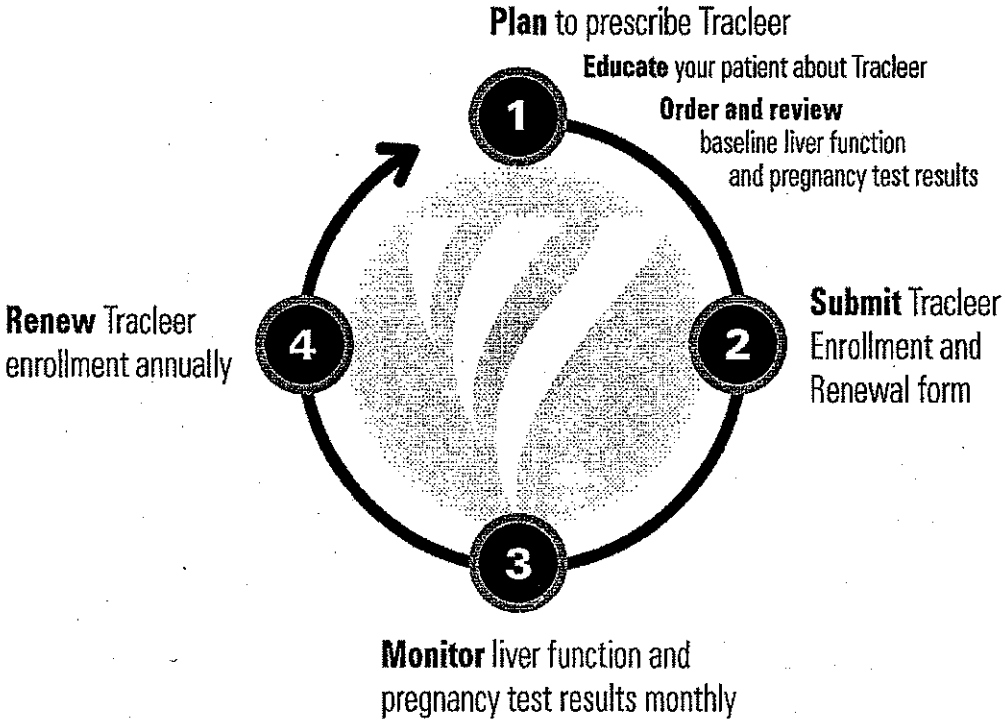
*Investigator-reported safety data obtained from 430 patients in placebo-controlled trials in PAH at doses of 125 mg BID or 250 mg BID.

Drug interactions[1]

- Tracleer is contraindicated for use with cyclosporine A and glyburide.
- Tracleer is metabolized by CYP2C9 and CYP3A.
  - Co-administration with agents that are metabolized by these pathways may affect plasma concentrations of one or both agents.
  - When initiating lopinavir/ritonavir and other ritonavir-containing HIV regimens, dosage adjustment of Tracleer is necessary.
  - When co-administered with simvastatin, or other statins that are CYP3A substrates, dosage adjustment of such statins may need to be considered.
  - When co-administered with rifampicin, a CYP3A inducer, liver function should be monitored weekly for the first 4 weeks before reverting to normal monitoring.
  - Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals; caution should be exercised if they are used together.
  - When co-administered with ketoconazole, a potent CYP3A inhibitor, no dose adjustment of bosentan is necessary, but increased effects of Tracleer may need to be considered.
- There are no clinically relevant interactions between Tracleer and warfarin, digoxin, nimodipine, losartan, or sildenafil.
  - Dose adjustments are not necessary when Tracleer and sildenafil are co-administered.
- Tracleer has no significant interaction with iloprost.

1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. 2009. **2.** Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896-903. **3.** Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet.* 2001;358:1119-1123.

4 ESSENTIAL steps to success



If you have questions about Tracleer enrollment and renewal, or if you would like more information about Tracleer, you can reach PAH Pathways, which administers T.A.P., by calling toll-free at 1-866-ACTELION (1-866-228-3546).

Please see accompanying full prescribing information.

PAHPathways™
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

Tracleer
BOSENTAN TABLETS

www.TRACLEER.com

ACTELION

[Month Day, Year]

Dear Valued Tracleer Prescriber:

Actelion has updated the way patients are enrolled for and maintained on Tracleer therapy. Because of the risks associated with Tracleer, including hepatotoxicity and teratogenicity, Actelion has updated the process of enrollment and renewal in the Tracleer Access Program (T.A.P.®) to ensure the ongoing safe use of Tracleer. While it is very similar to what you are accustomed to, there are some important changes.

What changes should you expect when prescribing Tracleer?

Renewal of Tracleer enrollment is now required annually. This entails a thorough review and discussion with your patients of the Medication Guide and the risks associated with Tracleer, and the submission of a completed Enrollment and Renewal form.

Prescriber certification is now required with each prescription (both initial enrollments and annual renewals). This involves confirming on the Tracleer Enrollment and Renewal form that you are aware of and have fulfilled essential steps that will help ensure the ongoing safe use of Tracleer.

As a certified Tracleer prescriber, you will continue to be required to educate your patients about the risks of Tracleer, the importance of monthly liver function and pregnancy testing, and the need for females of childbearing potential to use reliable methods of contraception (see definition and table on reverse side) and not to become pregnant. You also must continue to monitor your patients' liver function and pregnancy test results monthly, and counsel your patients as needed. Please remember that a patient receiving Tracleer can transition into a female of childbearing potential during the course of therapy.

As a certified prescriber of Tracleer, you may be contacted periodically to provide feedback regarding the effectiveness of T.A.P. to further ensure the ongoing safe use of Tracleer.

Enclosed is the new Essentials kit, which includes everything you need to enroll and renew your patients in T.A.P. The kit contains the following:

- Prescriber Essentials guide, with updated package insert
- New Tracleer Enrollment and Renewal forms
- Patient Essentials guides, which include the updated Medication Guide

Also enclosed is a copy of the letter that patients currently taking Tracleer will receive explaining the updated process.

Please see important safety information on the next page.

Tracleer
BOSENTAN TABLETS

ACTELION

Definition of female of childbearing potential

Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).

Reliable Methods of Contraception During Treatment with Tracleer

- Females of childbearing potential using Tracleer must use 2 reliable methods of contraception unless they have had a tubal sterilization or have a Copper T 380A IUD or LNg-20 IUS.

Methods to use alone	**Hormone** (choose 1 and use with a barrier method)	**Barrier** (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Transdermal patch —Vaginal ring • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

IMPORTANT SAFETY INFORMATION

Because of the associated risks, Tracleer may be prescribed only through the Tracleer Access Program. **Potential for serious liver injury** (including, after prolonged treatment, rare cases of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring)—Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter. **High potential for major birth defects**—Pregnancy must be excluded and prevented through the use of reliable forms of birth control; monthly pregnancy tests should be obtained.
Contraindicated for use with cyclosporine A and glyburide.

Please see accompanying full prescribing information.

Questions? Actelion is committed to making your transition to this updated process as smooth as possible. If you have any questions, please contact your local Tracleer representative or call PAH Pathways, which administers T.A.P., toll-free at 1-866-ACTELION (1-866-228-3546).

Sincerely,

Kirk Taylor, MD
Senior Vice President, Medical
Actelion Pharmaceuticals US

Tracleer
BOSENTAN TABLETS

FRM-549-COP-US

30+ Day Request and Justification Form

To: Specialty Pharmacy (fax #)

Request Date: _____

PATIENT INFORMATION

Name (First & Last): _____

Patient Registration #: AC _____ Date of Birth (MM/DD/YYYY): _____

Has the patient completed a minimum of three (3) months therapy with normal liver and/or pregnancy test results? YES NO

PRESCRIBING PHYSICIAN INFORMATION

Name (First & Last): _____

Office Contact: _____ Office phone #: ( ) _____ - _____

I, _____ request a supply of Tracleer of
Name of prescribing physician

2 Months 3 Months (not to exceed 3 months) for the above named patient for the following reason:
Travel outside the United States

I agree to accept the responsibility for monitoring the patient's blood tests for LFT and Pregnancy (if a female of childbearing potential) and to make those records available if necessary.

X _____
Prescribing Physicians Signature

Dear Doctor _____

We have received your request for a greater than 30-day supply of Tracleer (bosentan) for Patient Name.

As you may be aware Tracleer is typically shipped as a 30-day supply shipment. This was done to permit assure monthly liver and pregnancy testing before each shipment.

The FDA has approved a process whereby you can submit a written request for a greater than 30-day supply of Tracleer. This request must meet certain criteria and MUST NOT be for more than a 90-day supply.

We remind you that monitoring liver function and pregnancy status on a monthly basis is required. If your patient meets the criteria and is dispensed a greater than 30-day supply to travel outside of the US, you will be contacted in their place each month to determine if liver function testing has been completed. If the patient is a female of child bearing potential, you will be asked to confirm that pregnancy testing has been completed and she is utilizing reliable methods of contraception.

Please complete the enclosed 30+ Day Supply Request and Justification Form and fax it back to us at Fax #. Please allow as much lead-time as possible for review and processing. We will notify you of the outcome.

If you have any questions about the process, timing, or documentation, please contact us at Specialty Pharmacy Phone #.

Sincerely,

Name

TRACLEER SUPPLY – PATIENT INFORMATION SHEET

ATTENTION

Based on a request from your prescriber, we are sending you more than a 30-day supply of Tracleer.

While you are traveling outside of the United States, it is critical that you obtain liver function and pregnancy testing (if you are a female of childbearing potential) EVERY 30 days and have those tests reviewed by your prescriber to assure the results are acceptable. The proof of the testing and the results of those tests should be communicated to your prescriber in the US.

Tracleer can cause liver damage. Therefore you must have a blood test to check your liver function before you start Tracleer and each month after that. See the **"What is the most important information I should know about Tracleer?"** section of the Tracleer Medication Guide for information about the symptoms of liver problems.

Tracleer can cause serious birth defects if taken during pregnancy. You must not be pregnant when you start taking Tracleer or during Tracleer treatment. Serious birth defects from Tracleer can happen early in pregnancy. Females who are able to get pregnant must have a negative pregnancy test before starting and each month during Tracleer treatment.

Failure to have the tests done, and the results reviewed, could lead to medical problems. By requesting and accepting this shipment containing more than a 30-day supply of Tracleer, you have agreed to obtain liver function and pregnancy tests every 30 days, have them reviewed by a healthcare provider, and have the test results promptly reported to your healthcare provider in the US.

A copy of the full Prescribing Information is included with this supply. Please give it to the healthcare provider who arranges for and reviews your liver and pregnancy tests so that he or she has information on Tracleer.

Should you have ANY medical concerns or experience any side effects, contact your healthcare provider immediately.

PATIENT ESSENTIALS

Your guide to starting, taking, and renewing Tracleer

*Please see accompanying full prescribing information, including **BOXED WARNING** and Medication Guide.*

The Medication Guide starts on page 6 and is also enclosed in the back pocket.

PAH**Pathways**™
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

Tracleer
BOSENTAN TABLETS

Introduction to the essentials

This booklet describes how you and your healthcare provider will work together to ensure the safe use of Tracleer. Tracleer can cause liver damage if liver problems are not found early. Tracleer is likely to cause serious birth defects if taken during pregnancy.

To start treatment with Tracleer, you must review essential safety information with your healthcare provider, complete a Tracleer Enrollment and Renewal form, and agree to have important monthly tests. To continue therapy with Tracleer, you and your healthcare provider will renew your enrollment each year by completing another form.

As a patient taking Tracleer, you may be contacted periodically to provide feedback on your understanding of the risks associated with the use of Tracleer, and the importance of monthly liver and, if applicable, pregnancy testing.

Service and support essentials

Tracleer Access Program (T.A.P.®)

Because of the risks associated with treatment, you must be enrolled in T.A.P. to receive Tracleer. This is done when you and your healthcare provider complete the Tracleer Enrollment and Renewal form. T.A.P. is administered by PAH Pathways. PAH Pathways counselors coordinate with your certified specialty pharmacy to make sure you receive your Tracleer. You can learn more about specialty pharmacies on page 5.

You can reach PAH Pathways, which administers T.A.P., by calling toll-free at 1-866-ACTELION (1-866-228-3546).

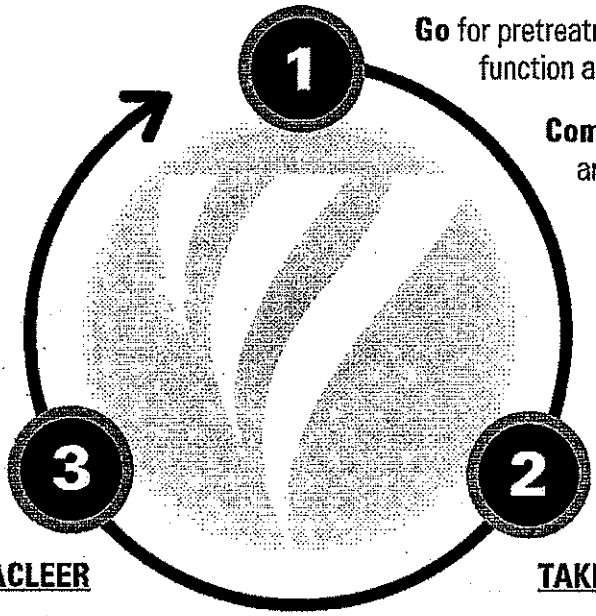
*Please see full prescribing information, including **BOXED WARNING** and Medication Guide, in the back pocket of this booklet.*

For patients with pulmonary arterial hypertension (PAH) WHO Class II-IV

Starting, taking, and renewing Tracleer

STARTING TRACLEER

Review the Medication Guide with your healthcare provider



Go for pretreatment liver function and pregnancy tests

Complete the Tracleer Enrollment and Renewal form with your healthcare provider

TAKING TRACLEER

Receive Tracleer from your specialty pharmacy

Go for monthly liver function and pregnancy tests

RENEWING TRACLEER

Renew Tracleer enrollment with your healthcare provider every year

Tracleer
BOSENTAN TABLETS

1 Starting Tracleer

> Review the Medication Guide with your healthcare provider

The Medication Guide starts on page 6 of this booklet, and it is also in the back pocket. It covers important facts about Tracleer that you must understand before you start therapy, including the risks of liver injury and serious birth defects. Talk with your healthcare provider if you have any questions.

> Go for your pretreatment liver function and pregnancy tests

Before you start Tracleer, you must have a blood test to check your liver function. You must also have a pregnancy test before you start Tracleer, if you are able to become pregnant. You should not start Tracleer if you are pregnant.

> Complete the Tracleer Enrollment and Renewal form with your healthcare provider

Before you start Tracleer, you must consent to be enrolled in the Tracleer Access Program (T.A.P.®) and agree to comply with the requirements of the program as outlined on the back of the Tracleer Enrollment and Renewal form.

Patient Agreement

- I have reviewed the Medication Guide with my healthcare provider. I understand that a Medication Guide will be provided to me each time I receive a prescription for Tracleer, and that I must read it each time because it may have new information important to my treatment.
- I have been informed of the risks of treatment with Tracleer, including the risks of liver injury and birth defects. I understand that I will be contacted by Actelion, its agents, and/or a healthcare provider to receive counseling on the risks of Tracleer treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for females of childbearing potential—see definition below) and, if I am a female who becomes pregnant, to obtain information about my pregnancy.
- I agree to notify Actelion or my specialty pharmacy if I should change prescribers.
- I agree to have monthly blood tests as ordered by my healthcare provider for as long as I take Tracleer.
- I authorize my healthcare providers, health plans, other payers, and pharmacies to disclose my personal, medical, and health information to Actelion Pharmaceuticals US, Inc., and its employees, distributors, agents, and contractors ("Actelion"), and I authorize Actelion to use and disclose this information for use in implementing T.A.P. including to 1) establish my benefit eligibility; 2) communicate with my healthcare providers, health plans, other payers, and pharmacies about my medical care; 3) provide support services, including facilitating the provision of Tracleer to me; and 4) help find ways to pay for Tracleer, or for treatment or healthcare operations in progress.
- I understand that I may be contacted by Actelion or its delegates regarding important safety surveys while I am taking Tracleer.
- I understand that Actelion does not promise to find ways to pay for my Tracleer, and I know that I am responsible for the costs of my care.
- I understand that once my health information has been disclosed to Actelion, privacy laws may no longer restrict its use or disclosure; however, Actelion agrees to protect my information by using and disclosing it only for the purposes described above or as required by law.
- I acknowledge and agree that, although Actelion will have access to my personal health information, Actelion will not be providing counseling or medical advice regarding my condition. I further understand that all questions regarding my medical and health conditions should be discussed with my healthcare provider.

2 Taking Tracleer

> Receive Tracleer from your specialty pharmacy

Tracleer is not available in your retail pharmacy; rather, it is carried by a limited network of certified specialty pharmacies that deliver Tracleer directly to you.

To reduce the risks of the use of Tracleer, you must have liver function and pregnancy tests each month (see below). Your specialty pharmacy will call you to confirm that you have had your tests before they deliver your Tracleer. The specialty pharmacies are required to document that you have had your tests each month.

If you don't confirm with your specialty pharmacy that you have had your tests or if you become pregnant, your specialty pharmacy will not be able to ship Tracleer to you and will contact your healthcare provider. It's important that you do not stop taking Tracleer unless your doctor tells you to do so. Suddenly stopping your treatment may cause your symptoms to get worse.

With each monthly delivery, you will receive a Medication Guide, which you should read each time because there may be new information.

> Go for monthly liver function and pregnancy tests

Each month, you must have a blood test to check your liver function. If you are able to become pregnant, you must also have a monthly pregnancy test. For more details about why these monthly tests are important and how to avoid becoming pregnant while taking Tracleer, please see the Medication Guide, which starts on page 6 of this guide.

3 Renewing Tracleer

> Renew Tracleer enrollment with your healthcare provider every year

In order to continue on Tracleer, you must start over again every year by reviewing the Medication Guide and completing the Tracleer Enrollment and Renewal form with your healthcare provider (step 1).

*Please see full prescribing information, including **BOXED WARNING** and Medication Guide, in the back pocket of this booklet.*

Tracleer
BOSENTAN TABLETS

Medication guide

Tracleer (tra-KLEER) (bosentan) Tablets

Read the Medication Guide that comes with Tracleer before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Tracleer?

Tracleer is only available through the Tracleer Access Program (T.A.P.). Before you begin taking Tracleer, you must read and agree to all of the instructions in T.A.P.

Tracleer can cause serious side effects including:

- **Liver damage**

  Liver damage may not cause symptoms at first. Only a blood test can show if you have early liver damage. You must have a blood test to check your liver function before you start Tracleer and each month after that. Your healthcare provider will order these tests. Regular blood tests are important because they will help your healthcare provider adjust or stop your treatment before there is permanent damage.

  Tell your healthcare provider if you have had liver problems, including liver problems while taking other medicines. Call your healthcare provider right away if you have any of these symptoms of liver problems while taking Tracleer:

  — nausea
  — vomiting
  — fever
  — unusual tiredness
  — stomach area (abdominal) pain
  — yellowing of the skin or the whites of your eyes (jaundice)

- **Serious birth defects**

  Tracleer can cause serious birth defects if taken during pregnancy. You must not be pregnant when you start taking Tracleer or during Tracleer treatment. Serious birth defects from Tracleer can happen early in pregnancy. Females who are able to get pregnant must have a negative pregnancy test before starting treatment and each month during Tracleer treatment.

Please see full prescribing information, including ***BOXED WARNING,*** *in the back pocket of this booklet.*

Talk with your healthcare provider or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. Do not have unprotected sex. Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.

Females who are able to get pregnant must use birth control (contraception) during Tracleer treatment. **You must choose and use 2 reliable forms of birth control at the same time, unless you have had a tubal sterilization, or have a Copper T 380A IUD or LNg 20 IUS. These methods can be used alone.**

Talk with your healthcare provider about which 2 methods of reliable birth control you should use. Your healthcare provider may recommend that you use a different method of birth control to help lower your risk of problems with your pulmonary arterial hypertension.

See the end of this Medication Guide for more information about reliable methods of contraception during treatment with Tracleer.

See "What are the possible side effects of Tracleer?" for more information about side effects.

What is Tracleer?

Tracleer is a prescription medicine used to treat people with certain types of pulmonary arterial hypertension (PAH), which is high blood pressure in the vessels of the lungs.

Tracleer can improve your ability to exercise and can slow the worsening of your physical condition and symptoms. Tracleer lowers high blood pressure in your lungs and lets your heart pump blood more efficiently.

Tracleer is only:

- prescribed by healthcare providers who are enrolled in T.A.P.
- available to people who understand and agree to enroll in T.A.P.

It is not known if Tracleer is safe and works in children below 12 years of age.

Medication guide (continued)

Who should not take Tracleer?

Do not take Tracleer if you:

- **are pregnant, plan to become pregnant, or become pregnant during Tracleer treatment. Tracleer can cause serious birth defects.** All females should read the **birth defects** section of "What is the most important information I should know about Tracleer?"
- have a blood test that shows possible liver injury.
- take one of these medicines:
  - cyclosporine A used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants
  - glyburide used for diabetes
- are allergic to any of the ingredients in Tracleer. See the end of this Medication Guide for a list of the ingredients in Tracleer. If you have a rash, hives or your lips swell after taking Tracleer, it may be a sign of allergy. You should stop taking your Tracleer and talk to your healthcare provider.

What should I tell my healthcare provider before taking Tracleer?

Tracleer may not be right for you. **Tell your healthcare provider about all your medical conditions, including if you:**

- **have liver problems.**
- **are breast-feeding or plan to breast-feed.** It is not known if Tracleer passes into your milk. You and your healthcare provider should decide if you will take Tracleer or breast-feed. You should not do both.

Please see full prescribing information, including ***BOXED WARNING,*** *in the back pocket of this booklet.*

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Tracleer and other medicines may affect how each other works and cause side effects. Especially tell your healthcare provider if you take:

- hormone-based birth control, such as pills, shots, patches, and implants. These birth control methods may not work as well when taken with Tracleer.
- simvastatin or other "-statin" medicines used to lower cholesterol
- rifampin used for tuberculosis
- tacrolimus used to prevent rejection of liver or kidney transplant
- ketoconazole, fluconazole, itraconazole, or voriconazole used for fungal infections
- warfarin sodium used to prevent blood clots
- ritonavir used to treat HIV

There may be more than one brand name medicine. Ask your healthcare provider if you are not sure if your medicine is one that is listed above.

How should I take Tracleer?

Your healthcare provider will give you detailed information about T.A.P.

- Tracleer will be mailed to you by a specialty pharmacy. You will only receive a 30-day supply of Tracleer at one time.
- Take Tracleer exactly as prescribed.
- Your healthcare provider will tell you how much Tracleer to take and when to take it.
- In most cases, you will take 1 tablet in the morning and 1 in the evening.
- You can take Tracleer with or without food.
- If you take more than the prescribed dose of Tracleer, call your healthcare provider right away.
- If you miss a dose of Tracleer, take your tablet as soon as you remember. Do not take 2 doses at the same time. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time.
- Do not stop taking Tracleer unless your healthcare provider tells you to. Suddenly stopping your treatment may cause your symptoms to get worse. If you need to stop taking Tracleer, speak with your healthcare provider about the right way to stop.

Medication guide (continued)

What are the possible side effects of Tracleer?

Tracleer can cause serious side effects, including:

- **See "What is the most important information I should know about Tracleer?"**
- **Fluid retention and swelling of your ankles and legs.** Tracleer can cause your body to hold too much water, and you may get swelling of your ankles and legs. Tell your healthcare provider if you have swelling of your ankles and legs that happens either with or without weight gain, or if you have more trouble with your breathing than normal. Your healthcare provider will look for the cause of this.
- **Lower sperm count.** Some men who take Tracleer may have lower sperm counts. This may affect your ability to father a child. Tell your healthcare provider if fertility is a concern for you.
- **Low red blood cell levels (anemia).** Your healthcare provider will do blood tests to check your red blood cells during treatment with Tracleer.

The most common side effects of Tracleer are:

- respiratory tract infection
- headache
- fainting
- flushing
- low blood pressure
- inflamed nose passages (sinusitis)
- joint pain
- irregular heartbeats

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Tracleer. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Tracleer?

- Store Tracleer at 68°F to 77°F (20°C-25°C).
- **Keep Tracleer and all medicines out of the reach of children.**

Please see full prescribing information, including ***BOXED WARNING,*** *in the back pocket of this booklet.*

General information about Tracleer

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Tracleer for a condition for which it was not prescribed. Do not give Tracleer to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Tracleer. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Tracleer that is written for health professionals. For more information, go to www.TRACLEER.com or call 1-866-228-3546.

What are the ingredients in Tracleer?

Active ingredient: bosentan.

Inactive ingredients: corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropylmethylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, ethylcellulose.

Reliable methods of contraception during treatment with Tracleer

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg 20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Transdermal patch —Vaginal ring • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

This Medication Guide has been approved by the U.S. Food and Drug Administration

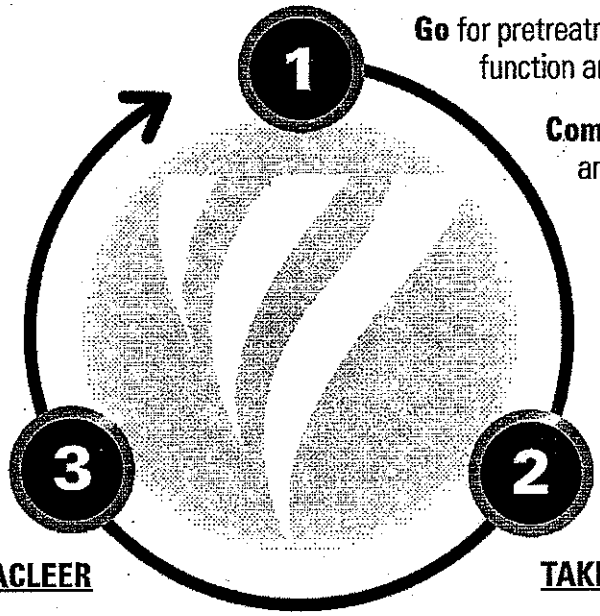
Revised August 2009

Tracleer BOSENTAN TABLETS

Starting, taking, and renewing Tracleer

STARTING TRACLEER

Review the Medication Guide with your healthcare provider



Go for pretreatment liver function and pregnancy tests

Complete the Tracleer Enrollment and Renewal form with your healthcare provider

TAKING TRACLEER

Receive Tracleer from your specialty pharmacy

Go for monthly liver function and pregnancy tests

RENEWING TRACLEER

Renew Tracleer enrollment with your healthcare provider every year

If you have questions about Tracleer enrollment and renewal, or if you would like more information about Tracleer, you can reach PAH Pathways, which administers T.A.P., by calling toll-free at 1-866-ACTELION (1-866-228-3546).

*Please see full prescribing information, including **BOXED WARNING** and Medication Guide, in the back pocket of this booklet.*

PAHPathways℠
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

BOSENTAN TABLETS

ACTELION

www.TRACLEER.com

EXHIBIT D

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-348

MEDICAL REVIEW

Medical Officer's Review of Response to Not Approved Letter

NDA#: 21-348
Drug: Zavesca (miglustat; OGT 918)
Sponsor: Oxford Glycosciences, Ltd.
Reviewer: Anne Pariser, M.D.
Date of Submission: 07-February-2003
Review Date: 16-June-2003

Re: Response to Not Approved (NA) Letter for NDA

I. Introduction and Background

The sponsor has submitted a response to a Not Approved (NA) letter from the initial NDA submission for Zavesca (miglustat; OGT 918): NDA 21-348; 000-B2, dated 07-February-2003. Zavesca has previously been reviewed under: NDA 21-348; 000, the initial NDA submission for Zavesca in the treatment of type 1 Gaucher disease. Zavesca has also been reviewed under: IND —— for types 1 —— Gaucher disease (active date 24-Apr-2000), IND —— for —— disease (active date 02-Dec-1998), IND —— for —— and under NDA 21-348. Please refer to the following reviews for additional background information on OGT-918:

1) NDA 21-348: Medical Officer's Review of NDA 21-348 (Gaucher disease type 1), dated 02-May-2002
2) IND 60,197: N-012-YY Annual Report (period 24-May-2001 to 19-November-2002), review dated 06-March-2003
3) IND 60,197: types 1 —— Gaucher disease (active date 24-Apr-2000)
4) IND —— —— disease (active date 02-Dec-1998)
5) IND —— (active date 04-Mar-2002)
6) IND —— (inactive 01-Jul-1998)
7) IND —— (inactive 30-Jun-1998)

Deficiencies were noted in the initial NDA, including Clinical, Pre-Clinical, and Chemistry issues. Only the Clinical issues will be addressed here. The Pre-Clinical and Chemistry issues will be deferred to the Chemistry and Animal Pharmacotoxicology Reviewers.

It is also noted that prior to the submission of the NA response by the sponsor, a meeting was held between the sponsor and the Division to address the deficiencies noted in the NA letter [please refer to the Meeting Minutes from this meeting (meeting date 24-September-2002)]. Briefly, agreement was reached between the sponsor and the Division that management of the risk/benefit ratio for Zavesca could be achieved through appropriate labeling and restricted use and distribution of the drug. The Division recommended that the labeling be revised to identify a target population who could not take enzyme replacement therapy (ERT), such as patients intolerant of ERT or patient with poor vascular access. The indication would, therefore, be revised to address patients

with this unmet medical need, and a restricted distribution of the drug is warranted to ensure that only the appropriately targeted population receive Zavesca.

II. Review of Response to NA

The sponsor's response to the NA consists of answers to the Clinical deficiencies listed in the NA letter from the Division, a revision of the proposed label, and additional clinical data as follows [please refer to sponsor's submission for complete details]:

- Efficacy Update for Study 001
- Safety Update: 240-day safety update with integrated safety data collected from NDA Studies 001, 003, and 004 (including extensions for these studies), and additional safety data from ongoing Studies 005 and 014.
- Restricted Distribution Plan
- Ongoing and Future Studies with Zavesca

Some of the information included in the Safety Update had previously been submitted and reviewed in the Annual Safety Update and Updated Investigator's Brochure for Zavesca, both of which were submitted 09-January-2003 (review date 06-March-2003). [Please see Appendix 2 for the Medical Review of the Annual Safety Update.]

A. Subject Exposure to Zavesca

The initial NDA submission for Zavesca included subjects exposed to Zavesca in Study 001 and extension (up to 24 months of treatment), Study 003 and extension (up to 12 months), and Study 004 and extension (up to 12 months). The subject exposures summarized in the Extended Use phase of these studies in the current submission include subjects exposed to Zavesca for >24 months to up to 48 months (> 91 to >156 weeks). The numbers of patients exposed to Zavesca for >91 weeks is limited. Eighteen (18) subjects had any exposure to OGT-918 >91 weeks: 14 subjects in Study 001 (starting dose 100 mg TID), 3 subjects in Study 003 (50 mg TID), and 1 subject in Study 004 (100 mg TID). Only 14 subjects had exposure to Zavesca of >117 weeks, all of whom were in Study 001. A summary of the Subject Disposition in the current submission is summarized in the following table

Table 1: Summary of Subject Disposition in the 240-Day Safety Update

	Number of Subjects in Safety Population Exposed to Zavesca					
	Study 001	Study 003	Study 004			Overall
	Zavesca 100 mg	Zavesca 50 mg	Zavesca 100 mg	Combination	Cerezyme, then Zavesca 100 mg	
Weeks						
0-26, n =	28	18	12	12	10	80
>26-52, n =	23	16	10	9	9	67
>52-78, n =	20	12	9	9	7	57
>78-91, n =	15	11	7	6	-	39
>91-117, n =	14	3	1	-	-	18
>117-130, n =	14	-	-	-	-	14
>130-156, n =	14	-	-	-	-	14
>156, n =	7	-	-	-	-	7

B. Efficacy Update

An efficacy update was submitted from the final 3-year analysis of Study 001. Subjects in Study 001 who were continued in the Extended Use phase of the study (beyond Month 12 of the original study) were allowed to continue only if the investigator felt that the subject would benefit from extended therapy. Thus, any subject continuing in the study was likely to have responded to treatment, and would have had to have demonstrated tolerance to study medication. Thus, both the efficacy and safety results of the Extended Use phase of Study 001 are to be interpreted with caution, and may not apply to all subjects treated *de novo* with Zavesca.

1. Patient Disposition for Study 001

Patient disposition for Study 001 was as follows:
28 patients were included in original study, of whom 22 patients completed 12 months of treatment, and 6 patients discontinued (2 for GI events, 2 for personal reasons, 2 for pre-existing conditions). Of the 22 patients who completed the initial 12 months of Study 001, 4 chose not to continue beyond Month 12, and 18 enrolled in the initial 12-month extension (Study 001X). Fourteen (14) of these 18 patients completed 24 months of study treatment, and 4 patients discontinued [2 for peripheral neuropathy, 2 as a precaution (same center as peripheral neuropathy patients)]. Fourteen (14) patients continued in the Extended Use phase of Study 001 beyond Month 24, all of whom completed 36 months of treatment. Eleven (11) of the 14 patients discontinued study medication between Months 36 and 48 (1 dementia syndrome and 10 remaining patients discontinued at the Israeli center where dementia syndrome was diagnosed. Note: the additional 10 patients were discontinued as the IRB placed the study on hold while the case of dementia was being investigated. The patient with dementia was further evaluated by a neurologist and was later diagnosed with Alzheimer's disease, which was not felt to be related to study medication.). Three (3) patients were ongoing as of Month 48.

2. Efficacy Results

The efficacy results for Study 001 up to Month 36 for liver and spleen volumes, platelet counts, and hemoglobin concentrations are summarized for the safety population, and for patients with any evaluable efficacy result using the last observation carried forward (LOCF) method.

a) Liver Volume

Efficacy results for changes from Baseline in liver volume show significant decreases in mean liver volume at all time points. The safety population showed progressive mean decreases in liver volume at Months 12 (n=21), 24 (n=12) and 36 (n=12) of –12%, -14% and –18%, respectively. However, on the LOCF analysis at Month 36, there was a mean decrease in liver volume of –15%, marginally lower than the –14% decrease seen at Month 24. The liver volume results are summarized in the following table

EXHIBIT E

APOTEX
ADVANCING GENERICS

From the desk of:
Shashank Upadhye, Esq.
VP, Global Intellectual Property
phone (416) 401-7701
fax (416) 401-3808
supadhye@apotex.com

21 January 2011

Mr. Perry Goldman, Esq.
V.P. – Legal Affairs & Compliance
Actelion Pharmaceuticals, Inc.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080
Fax:1 650 589 1501

Re: Access to Tracleer® (Bosentan) Samples

Dear Perry:

You may recall that we spoke quite a bit when you were at Elan and I was at Eon Labs/Sandoz during the metaxalone litigation, which I think is still ongoing. I am glad to see you have moved on to other ventures.

Apotex would like access to Tracleer® samples for it to investigate. Specifically and exercising all necessary controls, Apotex seeks:

- Tracleer Tablets 125 mg – 1800 tablets (60's bottle x 30 No.) (Apotex would request that equal quantity (30 bottles each) be supplied be from two different lots)
- Tracleer Tablets 62.5 mg – 420 tablets (60's bottle x 7 No.) from a single lot

These samples would be used to develop a generic equivalent of Tracleer Tablets to be submitted as an ANDA to the US FDA. The samples received would be used to analyzing the reference listed drug Tracleer® and also conducting bioequivalence studies to compare the Apotex Bosentan generic product and Tracleer Tablets. Apotex intends to develop this product for submission to USFDA as ANDA at its development facility Apotex Research Pvt Limited, located in Bangalore, India. The samples are not for commercial sale and will not be sold in the U.S. to any patient.

Apotex would be willing to pay the price per bottle at market value. Upon receipt of approval to access to the drug, Apotex would authorize its preferred wholesaler to procure the drug on its behalf to supply the drug to Apotex. All reasonably necessary controls will be put into place to control the access and handling of the bottles.

Please note that generic company access to a branded drug is an area of concern. See, "Generic-Drug Makers Protest Supply Limits", 12 Nov. 2009, Wall Street Journal (indicating that the FTC paying attention to access)(available here: http://online.wsj.com/article/SB10001424052748703808904574529690806933018.html) and see also, FDA Citizen Petition Docket No. 2009P-0266 (Dr. Reddy's Labs petition to access Revlimid).

Please call me if you have any questions. We appreciate a response in the next few weeks.

Regards,

Shashank Upadhye

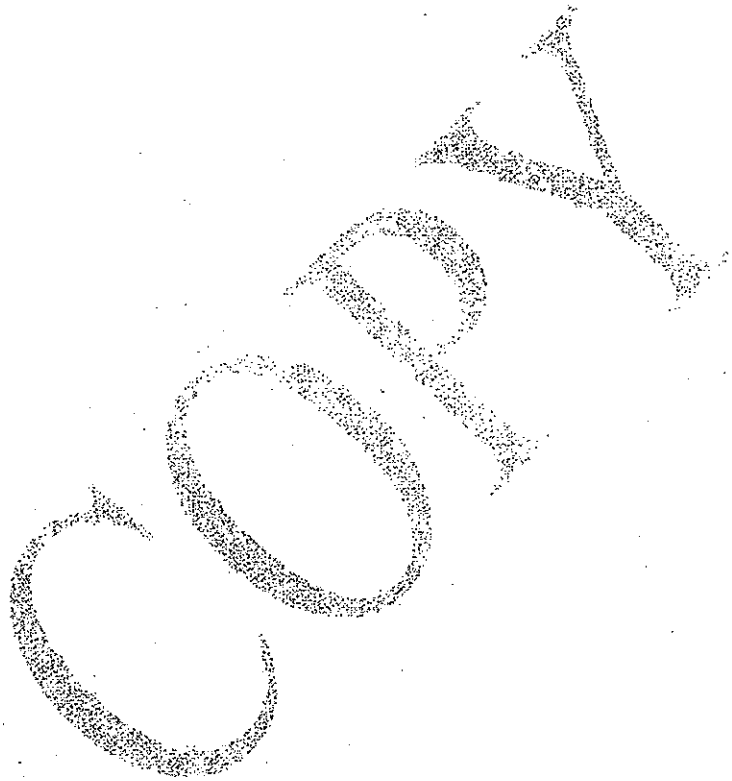


EXHIBIT F

APOTEX
ADVANCING GENERICS

From the desk of:
Shashank Upadhye, Esq.
VP, Global Intellectual Property
phone (416) 401-7701
fax (416) 401-3808
supadhye@apotex.com

12 April 2011

Mr. Perry Goldman, Esq.
V.P. – Legal Affairs & Compliance
Actelion Pharmaceuticals, Inc.
6000 Shoreline Court, Suite 200
South San Francisco, CA 94080
Fax:1 650 589 1501

Re: Access to Tracleer® (Bosentan) Samples

Dear Perry:

Concerning our letter in January 2011 to you, we have not yet heard back from Actelion on our request for access for samples. We reiterate our request for samples as again set forth below.

Apotex would like access to Tracleer® samples for it to investigate generic drug development. Specifically and exercising all necessary controls, Apotex seeks:

- Tracleer® Tablets 125 mg – 1800 tablets (60's bottle x 30 No.). Apotex would request that equal quantity (30 bottles each) be supplied from two different lots.
- Tracleer® Tablets 62.5 mg – 420 tablets (60's bottle x 7 No.) from a single lot.

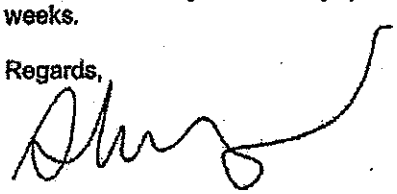
These samples will be used to investigate/experiment with and/or to develop a generic equivalent of Tracleer® Tablets to be submitted as an ANDA to the US FDA. The samples received would be used to analyze the reference listed drug Tracleer® and also conducting bioequivalence studies to compare the Apotex Bosentan generic product and Tracleer® Tablets. Apotex intends to develop this product for submission to the US FDA as ANDA from its development facility Apotex Research Pvt Limited, located in Bangalore, India. *The samples are not for commercial sale and will not be sold in the U.S. to any patient.*

Apotex would be willing to pay the price per bottle at market value. Upon receipt of approval to access to the drug, Apotex would authorize its preferred wholesaler to procure the drug on its behalf to supply the drug to Apotex. All reasonably necessary controls will be put into place to control the access and handling of the bottles.

Please note that generic company access to a branded drug is an area of concern. See, "Generic-Drug Makers Protest Supply Limits", 12 Nov. 2009, Wall Street Journal (indicating that the FTC is paying attention to access)(available here: http://online.wsj.com/article/SB10001424052748703808904574529890806933018.html) and see also, FDA Citizen Petition Docket No. 2009P-0266 (Dr. Reddy's Labs petition to access Revlimid). We wish to avoid entangling FDA with access issues.

Please call me if you have any questions. We appreciate a response in the next few weeks.

Regards,



Shashank Upadhye

EXHIBIT G

ZUCKERMAN SPAEDER LLP

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WASHINGTON, DC 20036-5802
202.778.1800 202.822.8106 fax www.zuckerman.com

AITAN D. GOELMAN
Partner
(202) 778-1996
agoelman@zuckerman.com

June 26, 2012

VIA FEDERAL EXPRESS

Mr. Perry Goldman
Vice-President – Legal Affairs & Compliance
Actelion Pharmaceuticals, Inc.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080

Re: Follow-up to requests to purchase Tracleer® samples for bioequivalence study to support ANDA

Dear Mr. Goldman:

This firm has been retained to represent Apotex, Inc., ("Apotex") in its efforts to obtain approval to market 125 and 62.5 mg generic bosentan tablets, which would compete with Actelion's Reference Listed Drug ("RLD") Tracleer®. As you know, as part of any Abbreviated New Drug Application ("ANDA"), the applicant must demonstrate bioequivalence with the RLD.

For this reason, on January 21, 2011, Apotex sent you a letter requesting to purchase samples of Tracleer® (bosentan) in sufficient quantities to investigate generic drug development. This letter explained that Apotex needed these samples in order to submit an ANDA to the United States Food and Drug Administration ("FDA") for a generic product; that Apotex was willing to pay the market price for these samples; that it would put into place all reasonably necessary controls to the access and handling of the drug under the Risk Evaluation Mitigation Strategy ("REMS") program; and that the samples were not for commercial sale. Nevertheless, Actelion never responded to this letter, a copy of which is attached for your convenience.

On April 12, 2011, Apotex sent you another letter reiterating its request. This letter, a copy of which is attached for your convenience, noted your failure to respond to the first letter and repeated that Apotex sought the Tracleer® samples in order to perform bioequivalence testing in support of an ANDA for a competing generic product. This letter reiterated Apotex's willingness to pay market price for the samples requested; to abide by all reasonably necessary controls to their access and handling; and Apotex's commitment that the samples would not be sold commercially. Nevertheless, you again failed to respond to Apotex's letter.

ZUCKERMAN SPAEDER LLP

Mr. Perry Goldman
June 26, 2012
Page 2

I am writing to renew Apotex's request for the necessary quantities of Tracleer®. As you are probably aware, Actelion may not deny access to its RLD to thwart efforts by generic manufacturers to bring competing products to market. It has already been 17 months since Apotex's first letter requesting Tracleer® samples for bioequivalence testing. You are no doubt aware of the economic harm caused Apotex by a delay in its submission of an ANDA to the FDA as a consequence of Actelion's refusal to make sufficient quantities of Tracleer® available for analysis and bioequivalence studies comparing the Apotex bosentan generic product to the RLD.

Please let us know within seven days whether Actelion is willing to provide Apotex the requested access to the samples of Tracleer®. Although Apotex would prefer to avoid litigation, it is unwilling to further delay its efforts to bring an important generic drug to market because of stonewalling on the part of Actelion.

Very truly yours,

Aitan D. Goelman
Sasha Miller

EXHIBIT H

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AITAN D. GOELMAN
Partner
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August 1, 2012

VIA E-MAIL
Mr. George G. Gordon
Dechert LLP
Cira Centre, 2929 Arch Street
Philadelphia, PA 19104-2808
george.gordon@dechert.com

Dear Mr. Gordon:

I write in response to your letter dated July 2, 2012, in which you, on behalf of your client, Actelion Pharmaceuticals ("Actelion"), refuse Apotex's request to purchase Tracleer® samples for bioequivalence ("BE") studies.

In your letter, you write that "Actelion has the right to choose with whom it does business and to whom it will sell products," and that "Actelion has concluded that it will not be fulfilling Apotex's request for Tracleer® tablets."

As you know, Actelion's "right to choose with whom it does business and to whom it will sell products" is not unlimited. As a monopolist, Actelion may not thwart competition by withholding drug samples that are necessary for generic pharmaceuticals to bring competing products to market. As mentioned in my letter to you of June 26, 2012, Apotex is unwilling to further delay its efforts to develop and seek FDA approval for a generic bosentan product.

I am enclosing a draft Complaint that Apotex has directed this firm to file against Actelion if Actelion continues to deny Apotex access to the Tracleer® samples that Apotex needs for its planned BE study. Please let me know by August 16, 2012, whether Actelion's position on Apotex's attempt to obtain these samples has changed. If it has not, please let me know whether you will accept service of the Complaint on behalf of Actelion.

Very truly yours,

Aitan D. Goelman

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA – SAN FRANCISCO DIVISION

APOTEX, INC. 150 Signet Drive Toronto, ON, M9L 1T9 Canada, Plaintiff, -against- ACTELION PHARMACEUTICALS, LTD. Gewerbestrasse 16 CH- 4123 Allschwill Switzerland, and ACTELION PHARMACEUTICALS U.S., INC. 5000 Shoreline Court, Suite 200 South San Francisco, CA 94080, Defendants.	**Case No.** **COMPLAINT FOR DAMAGES AND INJUNCTIVE RELIEF** **DEMAND FOR JURY TRIAL**

Plaintiff Apotex, Inc. ("Apotex"), by and through its undersigned counsel, files the following verified complaint against Defendants, Actelion Pharmaceuticals, Ltd., and Actelion Pharmaceuticals U.S., Inc., (collectively "Actelion"), seeking preliminary and permanent injunctive relief, declaratory relief and money damages, and states as follows:

NATURE OF THE ACTION

1. Actelion is the manufacturer of Tracleer®, a brand-name drug containing the active ingredient bosentan. Tracleer® is the only drug product of its kind (*i.e.*, with the active ingredient bosentan) approved for marketing by the United States Food and Drug Administration ("FDA"). Actelion therefore controls 100% of the commercial market for bosentan, the first oral treatment approved by the FDA for pulmonary arterial hypertension ("PAH"), a chronic and potentially life-threatening disease that severely compromises the functions of the lungs and the heart.

2. As part of the approval process for an abbreviated new drug application ("ANDA") under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), FDA requires drug manufacturers to conduct tests in order to demonstrate that their drug products are bioequivalent to the brand-name drug. Drug manufacturers seeking to develop generic versions of Tracleer® must therefore obtain sufficient samples of the brand-name drug to perform bioequivalence ("BE") testing.

3. Actelion has abused its monopoly power by denying Apotex the ability to purchase Tracleer® tablets for bioequivalence testing. As such, Actelion has been able to thwart the entry to market of any competing products, unlawfully maintaining its monopoly on bosentan.

JURISDICTION AND VENUE

4. This Court has subject matter jurisdiction over this case pursuant to 28 U.S.C. § 1331, in that this action involves federal questions arising under Section 2 of the Sherman Antitrust Act, 15 U.S.C. § 2, and the Declaratory Judgments Act, 28 U.S.C. §§ 2201, 2202.

5. Venue is proper in this Court as to Defendant Actelion Pharmaceuticals, Ltd. ("APL"), pursuant to the provisions of 28 U.S.C. § 1391(c)(3), in that APL is not resident in any judicial district and therefore may be sued in any judicial district.

6. Venue is proper in this Court as to Defendant Actelion U.S., Inc. ("Actelion U.S."), pursuant to the provisions of 28 US.C. § 1391 (b)(1) and (2), in that Actelion U.S. is subject to personal jurisdiction in this district at the time this action was commenced and thus resides in this district pursuant to 28 U.S.C. § 1391(c)(2), and in that this is a judicial district in which a substantial part of the events or omissions giving rise to the claim occurred.

INTRADISTRICT ASSIGNMENT

7. This action arises in San Mateo County because Actelion U.S. maintains its headquarters there, and a substantial part of the events or omissions giving rise to the claim occurred there. Assignment to the San Francisco Division is proper under Civil Local Rule 3-2(d), which provides that all civil actions which arise in San Mateo County shall be assigned to the San Francisco or Oakland Division.

THE PARTIES

8. Plaintiff Apotex is a Canadian pharmaceutical company. Founded in 1974, it is the largest producer of generic drugs in Canada. Apotex produces more than 300 generic pharmaceuticals and exports its products to more than 115 countries, including the United States.

9. Defendant Actelion Pharmaceuticals, Ltd. ("APL") is a multinational pharmaceutical company based in Allschwil/Basel, Switzerland. APL was founded in 1997, and its annual sales average almost $2 billion. APL has subsidiaries in more than 20 countries and employs approximately 2,500 employees, the largest number of whom are engaged in marketing.

10. Defendant Actelion Pharmaceuticals US, Inc. ("Actelion U.S.") is a subsidiary of APL. Actelion U.S. is incorporated in Delaware and maintains its headquarters in South San Francisco, CA. Actelion U.S. does business in every judicial district in the U.S.

BACKGROUND

FDA Approval for Brand-Name Drugs

11. Before marketing a new drug in the United States, a manufacturer must submit a New Drug Application ("NDA") to FDA, and FDA must approve it. Once approved, new drugs generally are referred to as brand-name drugs because they are marketed under a trade name or trademark for the drug product rather than under the chemical name of the drug product's active ingredient.

12. Among other things, an NDA must contain technical data on the composition of the drug product, including its active ingredient, the means for its manufacture and a statement of its proposed uses. FDA approves a new drug only if it determines, based on evidence submitted by the manufacturer, that the drug is safe and effective for its proposed use(s).

The Hatch-Waxman Amendments and Generic Drugs

13. Congress enacted the Hatch-Waxman Amendments ("Hatch-Waxman") to the FFDCA to increase the availability of low-cost generic drugs. A generic drug is a version of a brand-name drug that contains the same active ingredient as the brand-name drug, is generally sold without a trade name or trademark and typically sells at a lower cost than the brand-name drug.

14. Generic drugs are frequently prescribed in an effort to control healthcare costs. Generic drugs represent an increasing portion of the medicines used in the United States. The introduction of a generic drug as an alternative to a brand-name drug typically results in a

dramatic reduction in the brand-name drug's market share, particularly within the first six months.

15. The Generic Pharmaceutical Association estimates that from just 2001 through 2010, the nation's health care system saved $931 billion due to the use of generic drugs.

16. Before marketing a generic drug in the United States, a manufacturer must submit an ANDA to FDA, and FDA must approve it. An ANDA applicant must show that its generic drug is bioequivalent to the approved brand-name drug, known as the "reference listed drug" or "RLD." 21 U.S.C. § 355(j)(2)(A). The two drug products are considered bioequivalent if the rate and extent of absorption of the generic drug does not differ significantly from the rate and extent of absorption of the brand-name drug. FDA has established regulations and scientific guidance on how an applicant can demonstrate bioequivalence.

17. Under Hatch-Waxman, brand companies are required to submit patents claiming an approved drug to FDA for inclusion in the agency's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the "Orange Book."

18. A generic applicant must identify as part of its ANDA any patents listed in the Orange Book for the RLD and must certify as to each such patent (I) that no patent information has been filed with the FDA; (II) that the claimed patent has expired; (III) the date on which the filed patent will expire; or (IV) that the filed patent is invalid, unenforceable, or will not be infringed by the generic drug for which approval is sought ("Paragraph IV certification"). 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

19. As an incentive for generic applicants to challenge invalid, unenforceable, or non-infringed brand-company patents, Hatch-Waxman awards 180 days of marketing exclusivity to

the generic applicant that is first to file with, or as an amendment to, its ANDA a Paragraph IV certification with respect to any patent that the brand company asserts covers the RLD. 21 U.S.C. § 355(j)(5)(B)(iv). The exclusivity recipient is known as the "first filer."

20. For generic drug manufacturers, it is critically important to submit the first ANDA containing a Paragraph IV certification that is accepted by FDA for filing. Any delay in filing an ANDA, including one caused by the generic manufacturer's inability to perform bioequivalence testing in support of its ANDA due to a denial of access to the RLD, can result in a competitor being the first-to-file an ANDA containing a Paragraph IV certification. Historically, the generic drug manufacturer that is awarded 180-day marketing exclusivity for a particular drug captures the largest share of the generic market for that drug.

21. Even if a delay does not result in a competitor obtaining 180-day marketing exclusivity, every day of delay can cost the generic manufacturer severe economic injury.

Bosentan

22. Tracleer® is the brand-name drug containing the active ingredient bosentan.

23. Bosentan is a dual endothelin receptor antagonist. It works by blocking endothelin-1 (ET-1), a protein which causes blood vessels to narrow. Bosentan therefore causes blood vessels to expand and is used to treat PAH.

24. Tracleer® was approved by the FDA in 2001 for treatment of PAH. It was the first oral treatment approved for PAH.

25. Because PAH is a relatively rare condition, FDA designated Tracleer® as an orphan drug (a drug that is intended to treat a rare disease or condition). In order to encourage

manufacturers to develop treatments for relatively rare diseases, FDA offers makers of orphan drugs seven years of marketing exclusivity.

26. Under the Food and Drug Administration Amendments Act of 2007, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy ("REMS") from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. A REMS can include a requirement that restricts the distribution of the drug or biologic in question.

27. Use of bosentan has been associated with certain adverse reactions, including liver damage, the onset of anemia and birth defects when taken by pregnant women. Because of these potential side effects, the FDA required Actelion to institute a REMS when the agency approved Tracleer®. This includes monthly monitoring of liver functions and warning against use by pregnant women.

28. Tracleer® is extremely expensive, with an average monthly wholesale price of approximately $3,000. However, because of Actelion's monopoly power in this market, it has been able to maintain this premium pricing for Tracleer® since its inception.

29. Despite its status as an orphan drug, Tracleer® has been a blockbuster for Actelion, as sales of Tracleer® have accounted for a large majority of the company's revenues. Analysts following Actelion's stock have warned that, if and when the company loses its monopoly over bosentan without a follow-up product to take its place, this could be financially ruinous for the company. Actelion therefore has a pronounced incentive to maintain its monopoly over bosentan.

FACTUAL ALLEGATIONS

Apotex Researches, Develops and Identifies Generic Version of Bosentan

30. As part of its normal research into promising candidates for generic drugs, Apotex identified the opportunity and need for a generic equivalent to Actelion's RLD Tracleer®.

31. Apotex then developed a generic drug that it believed and believes is bioequivalent to Tracleer®.

32. Before marketing the drug in the United States, Apotex must submit, and obtain approval by the FDA of, an ANDA.

33. Before submitting an ANDA, Apotex must perform sufficient testing to demonstrate the bioequivalence between its generic product and Actelion's Tracleer®.

34. To demonstrate bioequivalence, Apotex must obtain a sufficient quantity of Tracleer®.

35. Tracleer® is therefore an essential facility, access to which is wholly controlled by Actelion.

Apotex Repeatedly Attempts to Acquire Tracleer® for BE Testing

36. On January 21, 2011, Apotex sent Actelion a letter requesting to purchase Tracleer® samples for BE testing. The letter was sent to Actelion U.S.'s headquarters in South San Francisco.

37. In this letter, a copy of which is attached as Exhibit A, Apotex noted the quantity and amounts of Tracleer® that it sought to purchase, and noted further as follows:

- The samples sought "would be used to develop a generic equivalent of Tracleer® Tablets to be submitted as an ANDA to US FDA. The samples received would be

used to analyzing [sic] the reference listed drug Tracleer® and also conducting bioequivalence studies to compare the Apotex Bosentan generic product and Tracleer® Tablets. Apotex intends to develop this product for submission to the USFDA as ANDA."

- The samples were "not for commercial sale and will not be sold in the U.S. to any patient."
- Apotex was "willing to pay the price per bottle at market value," and "[a]ll reasonably necessary controls will be put into place to control the access and handling of the bottles."

38. Although Apotex noted that it would "appreciate a response in the next few weeks," Actelion never responded to the letter.

39. On April 12, 2011, having received no response to its previous request, Apotex sent another letter to Actelion, a copy of which is attached as Exhibit B, repeating its request to purchase samples of Tracleer® for BE testing.

40. This second letter repeated Apotex's commitment to exercise all reasonably necessary controls over the samples and noted again, "*[t]he samples are not for commercial sale and will not be sold in the U.S. to any patient.*" (emphasis in the original).

41. The letter again explained that Apotex was seeking the samples of Tracleer® in order to conduct BE testing on a generic competitor for inclusion in an ANDA and repeated Apotex's willingness to pay market price for the samples.

42. This second letter noted that Apotex had "not yet heard back from Actelion," and that this missive was designed "to reiterate our request for samples as again set forth below."

43. Although this letter also asked for a response "in the next few weeks," Actelion never responded to this letter, either.

Apotex Attempts to Use the Canadian Equivalent of Tracleer® for BE Testing

44. Also on April 21, 2011, Apotex submitted a letter to the FDA's Office of Generic Drugs ("OGD") describing its attempts to procure Tracleer® from Actelion (as well as a second RLD from a different manufacturer). Apotex further informed OGD that it had been able to procure samples of the Canadian version of Tracleer®, which was also manufactured by Actelion, and argued that the Canadian version of Tracleer® was an appropriate substitute for the U.S. RLD for the purpose of BE testing. Finally, Apotex told OGD that, because of its inability to procure samples of the RLD in the United States, Apotex intended to conduct a BE study against the Canadian version of the drug and submit the results of this testing in support of an ANDA for a generic alternative to Tracleer®. Apotex asked for the FDA's "feedback on the issue at the earliest to ensure that we can plan appropriately to submit the ANDAs on time."

45. On May 10, 2011, Apotex submitted a BE study protocol to OGD. Consistent with Apotex's stated intent, the BE protocol submitted proposed using Tracleer® from Canada or Europe for the study.

46. On February 21, 2012, the OGD Division of Clinical Review sent Apotex its comments on Apotex's proposed BE study protocol for bosentan tablets. Although the agency agreed with the suggestion in Apotex's proposed protocol that the study only involve male subjects to minimize the risk of fetal exposure to bosentan, it recommended certain changes to the protocol in order to ensure that the controls constituted an adequate substitute to those in the FDA-mandated REMS governing access to Tracleer®.

47. In its response, the OGD noted that the review by the Division of Clinical Review was conducted exclusively for safety and that comments on the design of the BE study were referred to the OGD's Division of Bioequivalence II.

48. On May 21, 2012, the OGD Division of Bioequivalence II provided its comments on the proposed BE study protocol submitted by Apotex on May 10, 2011. The FDA stated that the proposed protocol was acceptable, provided that Apotex adopted a number of recommendations.

49. All of OGD's recommendations were easily incorporated into Apotex's proposed BE study save one, the recommendation that the studies "should be performed using the approved US product as the reference product. It is not acceptable to use an approved Canadian drug product as described in your protocols." Because of Actelion's refusal to sell Apotex the requested samples of Tracleer®, Apotex has been unable to procure "the approved US product" to use in its BE study, as directed by the FDA.

Counsel for Apotex Attempts to Acquire Tracleer® Samples for BE Testing

50. Given the FDA's insistence that Apotex acquire, and use, samples of the U.S. RLD Tracleer® for the BE study, Apotex tried, for a third time, to obtain these samples from Actelion.

51. On June 26. 2012, counsel for Apotex sent a letter, attached as Exhibit C, to Actelion reprising Apotex's previous request for sufficient quantities of Tracleer® to conduct a BE study.

52. Counsel for Apotex noted that Actelion had never responded to Apotex's prior attempts to procure Tracleer® for BE testing, and that Apotex was willing to pay market price for the samples and to implement all reasonably necessary controls for the access and handling of Tracleer under the REMS. Counsel further noted the impropriety of Actelion denying access to its "RLD to thwart efforts by generic manufacturers to bring competing products to market," and that it had been 17 months since Apotex had first requested that Actelion sell Apotex

samples of Tracleer® for BE testing. Counsel stated that this delay was causing Apotex economic harm by delaying Apotex's submission of an ANDA for a competing generic bosentan product. Finally, counsel noted that, while Apotex preferred to avoid litigation, it was "unwilling to further delay its efforts to bring an important generic drug to market because of stonewalling on the part of Actelion."

53. Counsel for Actelion responded by letter dated July 2, 2012. In this letter, Actelion flatly refused to provide Apotex with samples of Tracleer® for BE testing, claiming that Actelion "has the right to choose with whom it does business and to whom it will sell its products."

54. Although Actelion's letter cited the existence of the Tracleer® REMS, which it argued "does not provide for the sale of Tracleer tablets to Apotex," counsel for Actelion made clear that Actelion's claimed right not to sell Tracleer® samples to Apotex "exists independently of the REMS program for Tracleer, and [that Actelion] has concluded that it will not be fulfilling Apotex's request for Tracleer tablets."

COUNT I

(Violation of Section 2 of The Sherman Act)

55. Apotex incorporates by reference paragraphs 1 through 54 above as if set forth in full.

56. It is impossible for a generic manufacturer like Apotex to bring a competing bosentan product to market without access to Tracleer® for bioequivalence testing. Tracleer®, the distribution of which is controlled by Actelion, is thus an essential facility for the production of generic bosentan, and Actelion is a monopolist with control over this essential facility.

57. The relevant market of Actelion's monopoly is the market for bosentan in the United States, and the market for orally administered pharmaceuticals for treatment of PAH.

58. By refusing to provide samples of Tracleer® to Apotex to perform the BE testing necessary to submit an ANDA for generic bosentan, Actelion has controlled an essential facility necessary for the production of bosentan, thereby effectively maintaining its monopoly, in violation of Section 2 of the Sherman Act, 15 U.S.C. § 2.

59. Actelion's refusal to provide samples of Tracleer® for bioequivalence testing was intended to, and did, extend its monopoly in the relevant markets, also in violation of Section 2 of the Sherman Act, 15 U.S.C. § 2.

60. Actelion's maintenance of its unlawful monopoly has had the effect of delaying the entry of a generic competitor for many months, during which time:

a. Competition in the manufacture, sale and distribution of bosentan was restrained, suppressed and eliminated;

b. Actelion reaped monopolist's profits in an amount to be determined at trial from its sale of Tracleer®;

c. Apotex forewent revenue that it otherwise would have earned from the sale of generic bosentan in an amount to be determined at trial; and

d. Patients who purchased Tracleer® were forced to pay artificially high, monopolist's prices, for bosentan.

COUNT II

(Mandatory Injunctive Relief)

61. Apotex incorporates by reference paragraphs 1 through 60 above as if set forth in full.

62. Apotex has a reasonable probability of success on the merits.

63. Apotex's right to relief in the form of access to sufficient samples of Tracleer® to enable it to perform bioequivalence testing in support of an ANDA is clear.

64. As a result of Actelion's unlawful conduct, as alleged herein, Apotex will continue to suffer immediate and irreparable harm that cannot be fully remedied by money damages.

65. Apotex does not have an adequate remedy at law.

66. Granting immediate injunctive relief to Apotex will not result in greater harm to Actelion.

67. Granting immediate injunctive relief to Apotex will be in the public interest, as it will finally allow the pursuit of lower-cost, generic competitors to an important drug used to treat a potentially fatal disease, resulting in competition in the relevant product and geographic markets.

68. Apotex is entitled to a mandatory immediate injunction pursuant to 15 U.S.C. § 26 and Fed. R. Civ. P. 65, requiring Actelion to provide Apotex with the following quantities of Tracleer® tablets for bioequivalence testing:

a. 1800 tablets (60 bottles, including 30 bottles each from two different lots) of 125 mg. Tracleer® tablets.

b. 420 tablets from a single lot of 62.5 mg. Tracleer® tablets.

COUNT THREE

(Declaratory Relief)

69. Apotex incorporates by reference paragraphs 1 through 68 above as if set forth in full.

70. Apotex seeks to submit an ANDA to manufacture generic bosentan. The FDA OGD has stated that this ANDA must demonstrate BE based on BE studies performed using the RLD (i.e., FDA-approved) Tracleer®.

71. Apotex has requested that Actelion provide Apotex with sufficient samples of Tracleer® to perform this BE testing, and has indicated that it will pay Actelion market price for these samples and will take all reasonably necessary and appropriate precautions in handling the drug.

72. Nevertheless, Actelion has refused to provide samples of Tracleer® to Apotex and has claimed that it has no obligation to provide Tracleer® to Apotex.

73. Thus, a dispute currently exists between Actelion and Apotex with respect to Actelion's obligation to provide Apotex with samples of Tracleer® to use for BE testing.

74. Apotex is therefore entitled, pursuant to the Declaratory Judgments Act, 28 US.C. §§ 2201 and 2202, to a declaration of rights and obligations whereby Actelion is obliged to provide samples of Tracleer® to Apotex for use in the BE testing necessary to support an ANDA for a generic bosentan product.

PRAYER FOR RELIEF

WHEREFORE, Apotex respectfully requests judgment in its favor and against Actelion as follows:

a) Granting preliminary and permanent mandatory injunctive relief pursuant to 15 U.S.C. § 26 and Fed. R. Civ. P. 65 compelling Actelion to provide Apotex with 1800 Tracleer® 125 mg. tablets (in equal quantities from two different lots) and 420 Tracleer® 62.5 mg. tablets (from a single lot);

b) Compensatory damages for Apotex's lost sales of generic bosentan and profits on those sales;

c) Treble damages pursuant to 15 U.S.C. § 15;

d) An award of attorneys' fees and costs pursuant to 28 U.S.C. § 15;

e) A declaration that Actelion is required to provide Apotex with samples of Tracleer® in the quantity and pursuant to the specifications set forth above;

f) Such other and further relief as the Court deems just and proper.

JURY DEMAND

Plaintiff demands a trial by jury on all issues so triable.

Dated: August __, 2012

Respectfully submitted,

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Ismail J. Ramsey (CA Bar No. 189820)
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EXHIBIT I

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AITAN D. GOELMAN
Partner
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August 17, 2012

VIA E-MAIL

Mr. George G. Gordon
Dechert LLP
Cira Centre, 2929 Arch Street
Philadelphia, PA 19104-2808
george.gordon@dechert.com

Dear Mr. Gordon:

Thank you for your letter dated August 9, 2012. Apotex continues to disagree with Actelion's position that it has the right to deny Apotex the opportunity to purchase samples of the RLD Tracleer® in sufficient quantities to perform the BE study necessary to file an ANDA to bring a generic competitor to market. Moreover, several of Actelion's requests for "clarification" appear unrelated to a good faith evaluation of Apotex's request and instead seem calculated to allow Actelion to obtain proprietary or strategic information belonging to Apotex, to which Actelion is not entitled. Nevertheless, in a final effort to avoid litigation, Apotex addresses several of Actelion's concerns, below.

First, Apotex recognizes Actelion's "legitimate interests" in complying with the Tracleer® REMS program. Apotex addressed the restrictions in the REMS in the proposed BE protocol that it submitted to the FDA's Office of Generic Drugs ("OGD") on May 10, 2011, to which the OGD responded on February 21, 2012 (see Draft Complaint, at ¶¶ 45-47). As the Draft Complaint recites,[1] OGD recommended certain changes in the proposed protocol to ensure that it contained controls adequate to substitute for the restrictions in the Tracleer® REMS themselves. These changes included the following recommendations: providing the personnel administering the BE study with the Tracleer Access Program ("T.A.P.") "Prescriber Essentials" training guide; notifying Actelion of any adverse events; documented testing of liver functioning for each subject who received Tracleer®; providing each subject with the T.A.P. "Patient Essentials" guide; counseling subjects about the potential risks of Tracleer®; excluding illiterate

[1] Apotex declines Actelion's invitation to provide it with copies of the correspondence between Apotex and the FDA regarding bosentan, to which Actelion is not entitled. We have described the relevant aspects of the correspondence in the Draft Complaint and in this letter. Actelion does not need to review copies of the correspondence, which contain proprietary or strategic information belonging to Apotex, to make a good-faith evaluation of Apotex's request to purchase samples of Tracleer®.

ZUCKERMAN SPAEDER LLP

subjects unable to read the Informed Consent; and tracking additional details about safety and tolerability monitoring. Notably, Apotex is committed to making each of the changes recommended by the FDA so that the safety controls for the BE study are at least as robust as those in TAP itself.

Second, you asked "why the FDA rejected the use of samples from Canada in Apotex's BE protocol." As set forth in the Draft Complaint, at ¶ 44, after Apotex was unable to procure samples of the U.S. RLD Tracleer®, Apotex attempted to persuade the FDA that the Canadian version of Tracleer® was an appropriate substitute for the purpose of BE testing. As further set forth in the Draft Complaint, at ¶ 49, the FDA rejected that argument, stating that the BE study should use "the approved U.S. product as the reference product. It is not acceptable to use an approved Canadian drug product as described in your protocols." The FDA's response did not elaborate on this insistence that the U.S. RLD be used for the BE study.

Third, you ask under what paragraph of 18 U.S.C. 355(j)(2)(A)(vii)(I)-(IV) Apotex intends to file its ANDA for generic bosentan, and whether Apotex's product would "infringe Actelion's intellectual property covering Tracleer, including but not limited to" the '740 Patent. This inquiry has nothing to do with Actelion's purported right to refuse Apotex the opportunity to purchase samples of Tracleer®. Should Actelion believe that any product for which Apotex ultimately seeks FDA approval infringes its intellectual property, it will have the same legal remedies available to it as the holder of any other patent.

In your letter, you note that, while Actelion is "willing to take" Apotex's responses to your questions "into account," you "cannot promise" that they "will necessarily change Actelion's position." Please understand that, for Apotex's part, while it was willing to defer filing a lawsuit while it attempted to address at least those questions of Actelion that were arguably relevant to Apotex's request, it is not willing to delay any further, since it is suffering economic harm each day that Actelion withholds the requested samples of Tracleer®. For this reason, Apotex is unwilling to engage in further back-and-forth with Actelion regarding its request. I therefore ask that you notify me no later than August 25, 2012, whether Actelion is willing to provide Apotex with the Tracleer® samples. If it is not, please let me know whether you are authorized to accept service of the complaint.

Very truly yours,

Aitan D. Goelman

EXHIBIT J

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July 2, 2012

VIA E-MAIL

Aitan D. Goelman, Esquire
Zuckerman Spader LLP
1800 M Street, NW
Washington, DC 20036-5802

Re: Requests to purchase Tracleer samples

Dear Mr. Goelman:

I am writing in response to your letter to Perry Goldman dated June 26, 2012 requesting Tracleer tablets on behalf of Apotex, Inc. ("Apotex").

Your letter incorrectly suggests that Actelion is somehow required by law to sell Tracleer to Apotex. Actelion's Risk Evaluation and Management Strategy ("REMS") for Tracleer, however, does not provide for the sale of Tracleer tablets to Apotex. Moreover, as I am sure you are aware, Actelion has the right to choose with whom it does business and to whom it will sell its products. Actelion reserves that right, which exists independently of the REMS program for Tracleer, and has concluded that it will not be fulfilling Apotex's request for Tracleer tablets.

If you would like to discuss this further, please direct any further correspondence or communications on this matter to me.

Sincerely,

George G. Gordon

GGG:jz

EXHIBIT K

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August 9, 2012

VIA E-MAIL

Aitan D. Goelman, Esquire
Zuckerman Spader LLP
1800 M Street, NW
Washington, DC 20036-5802

Dear Mr. Goelman:

I am writing in response to your letter dated August 1, 2012. For reasons explained in my letter of July 2, 2012, Actelion does not have an obligation to provide Apotex, Inc. with samples of patent-protected Tracleer tablets. To safeguard patient safety, the FDA required that distribution of Tracleer be strictly limited pursuant to a Risk Evaluation and Mitigation Strategy ("REMS"). As a matter of law, Actelion must comply with the FDA-mandated REMS program covering Tracleer. Apotex, Inc. has not addressed this issue. Actelion also has an independent right to decide with whom it will do business and, although you suggest that this right is "not unlimited," none of the very rare exceptions to that right exist here.

Nothing in your letter, or draft complaint, has changed Actelion's views in this regard, but Actelion is willing to evaluate Apotex's request that it reconsider its position. Among the concerns underlying Actelion's decision not to supply Tracleer samples to Apotex are Actelion's legitimate interests in complying with its REMS program's strict limitations on distribution and protecting its intellectual property. It would therefore help to understand the following:

1. Would Apotex's potential generic formulation infringe Actelion's intellectual property covering Tracleer, including but not limited to United States Patent Number 5,292,740 (the "'740 Patent")? If not, please explain why not.

2. Does Apotex intend to file an ANDA with a Paragraph IV certification, challenging the infringement, validity and/or enforceability of the '740 Patent, and forcing the parties to litigate these issues?

3. Alternatively, does Apotex intend to file a Paragraph III certification, seeking approval only after the '740 Patent expires in November 2015?

Dechert LLP

4. Why the FDA rejected the use of samples from Canada in Apotex's BE protocol. To further assist Actelion in evaluating your request, please provide copies of Apotex's correspondence with the FDA on this issue, including those communications referenced in paragraphs 44-49 of the draft Complaint.

I cannot promise that Apotex's responses to these questions will necessarily change Actelion's position, but Actelion is willing to take them into account in evaluating your request.

Sincerely,

George G. Gordon

George G. Gordon

GGG:jz

EXHIBIT L

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August 21, 2012

VIA E-MAIL

Aitan D. Goelman, Esquire
Zuckerman Spader LLP
1800 M Street, NW
Washington, DC 20036-5802

Dear Aitan:

Thank you for your letter of August 17, 2012. At the outset, I appreciate Apotex's acknowledgment of Actelion's legitimate interest in complying – and assuring that others with access to Tracleer from Actelion comply – with the Tracleer REMS program. Unfortunately, Apotex's position, reflected in the August 17 letter, raises more questions than it answers, and highlights precisely the basis for Actelion's concerns about REMS compliance. For example, you assert that the FDA's Office of Generic Drugs ("OGD") recommended changes to Apotex's proposed protocol "to ensure that it contained controls adequate to substitute for the restrictions in the Tracleer REMS themselves." Yet Apotex is unwilling to specify precisely the controls that it proposes to have in place or to provide the correspondence with the FDA documenting the controls required by the FDA and acceded to by Apotex. Similarly, you assert that Apotex is "committed to making" these changes, which I assume – correct me if I am wrong – means that Apotex has yet to incorporate them into its BE protocol or to submit them to the FDA for review. Thus, as things stand, Actelion is unable to confirm that OGD suggested changes, what those changes were or how they will be reflected in Apotex's final BE testing protocols. In effect, the message from Apotex to Actelion is simply "trust me." For several reasons, that is simply not an adequate response.

First, Actelion is under an FDA-mandated obligation to comply with restrictions on distribution reflected in the REMS. Apotex has not provided any communication from the FDA to support Apotex's demand that Actelion depart from the REMS. In effect, Apotex is insisting that Actelion violate its REMS obligations based solely on Apotex's say-so. That is simply unreasonable on its face. In addition, Apotex's BE testing will require it to manage the administration of Tracleer samples to patients, which – if the proper safeguards are not put in place by Apotex – could have serious consequences for Actelion separate and apart from REMS compliance. It is not reasonable to expect Actelion to assume potentially significant risks based on nothing more than Apotex's assurance that it is committed to implementing OGD's suggested changes.

Dechert LLP

Actelion, however, still remains open to considering Apotex's request for samples with which to conduct bioequivalence testing. To do so, Actelion will need the following, at a minimum, to confirm that supply of Tracleer tablets will not violate Actelion's REMS obligations or otherwise subject Actelion to other unacceptable risks:

(1) Apotex's final testing protocols to insure that it indeed incorporates the necessary safeguards consistent with the Tracleer REMS, and which are necessary to deal with other risks associated with administering Tracleer to study participants.

(2) Written confirmation from the FDA that it would be acceptable under the REMS for Actelion to supply Apotex with Tracleer samples for use in BE testing consistent with the final protocols.

We will also need to deal with the other issues raised in my letter of August 9, 2012. You assert that Actelion's concern regarding its intellectual property "has nothing to do with Actelion's purported right to refuse Apotex the opportunity to purchase samples of Tracleer." Apotex, however, is suggesting that Actelion is required, as a matter of law, to sell it a patented product. Actelion's intellectual property is plainly relevant to its right to refuse such a request.

In our view, continuing our letter-writing campaign is not likely to be productive to resolving these issues. Instead, we propose a face-to-face meeting. Please let me know if you are available tomorrow or Thursday to meet in Washington. If those days do not work on your end, please propose some alternatives.

Best regards,

George G. Gordon

George G. Gordon

GGG:jz

EXHIBIT M

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

January 12, 2012

Shal Jacobovitz
President
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080

Dear Shal,

Roxane Laboratories, Inc. (RLI) respectfully submits this request to purchase Tracleer directly from Actelion Pharmaceuticals US, Inc.

RLI acknowledges that distribution of TRACLEER® Tablets 62.5 and 125mg are normally controlled through a restricted distribution system as part of Actelion's Risk Evaluation and Mitigation Strategy (REMS) known as Tracleer Access Program (T.A.P.). Because our request does not lend itself to the process outlined in T.A.P. we are requesting to purchase TRACLEER® Tablets 62.5 and 125mg for our development directly from Actelion.

The purchased product will be used solely for developmental purposes to meet FDA requirements in support of an ANDA filing.

Initially, RLI would like to order an amount of material for in vitro use only.

As a courtesy, please respond to our request within 30 days. If you would like to discuss this request in greater detail, please contact me at (614) 272-4799.

Sincerely,

Randall S. Wilson
Vice President, Scientific, Regulatory, and Medical Affairs
Roxane Laboratories, Inc.

cc: Perry Goldman, Vice President, Legal Affairs and Commercial Compliance

EXHIBIT N

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Karen N. Walker, P.C.
To Call Writer Directly:
(202) 879-5096
karen.walker@kirkland.com

August 1, 2012

VIA FED EX

Colleen T. Sullivan
Assistant Director, Legal Affairs
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080

Re: Tracleer Tablet Sample Supply

Dear Ms. Sullivan:

Your letter of February 10, 2012 to Randall Wilson of Roxane Laboratories, Inc. ("Roxane") has been forwarded to me.

On behalf of my client Roxane, I urge you to reconsider your position regarding Roxane's efforts to purchase research quantities of Tracleer for development purposes.

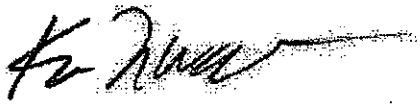
Roxane has been unable to purchase this product, as it normally does in the ordinary course of business, from pharmaceutical wholesalers due to Actelion's restrictions. Accordingly, Roxane requested to purchase supply from Actelion directly.

You assert that Actelion has the right to sell to whom it chooses, but it is Actelion's refusal to sell *combined with* the restriction on others, including customary wholesalers, to sell to Roxane that is anticompetitive. In short, Actelion not only refuses to sell such product to Roxane directly, but Actelion also precludes distributors from selling such samples to Roxane as well, despite the express prohibition in the FDAAA against using REMS restrictions "to block or delay approval" of generic applications. This conduct violates Sections 1 and 2 of the Sherman Act as well as applicable state competition and unfair trade practice laws.

Roxane intends to pursue all available options, including notifying the Federal Trade Commission and/or asserting antitrust and related claims against Actelion.

The purpose of my letter is to explore alternatives to such legal options, including arrangements that we have successfully negotiated in previous situations with other brand name pharmaceutical companies. We are able to demonstrate ability to comply with all legitimate safety concerns and do not insist on being able to purchase supplies directly from Actelion as long as it does not use distribution restrictions to impede Roxane's ability to purchase product for development purposes from normal distribution channels.

Sincerely,



Karen N. Walker, P.C.

cc: Andrea J. Kochensparger

EXHIBIT O

Dechert LLP

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Philadelphia, PA 19104-2808
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www.dechert.com

GEORGE G. GORDON

george.gordon@dechert.com
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August 9, 2012

VIA E-MAIL

Karen N. Walker, P.C.
Kirkland & Ellis LLP
655 Fifteenth Street, N.W.
Washington, DC 20005

Dear Karen:

I am writing in response to your letter dated August 1, 2012 to Colleen Sullivan. For reasons explained in Ms. Sullivan's letter of February 10, 2012, Actelion does not have an obligation to provide Roxane Laboratories, Inc. with samples of patent-protected Tracleer tablets. To safeguard patient safety, the FDA required that distribution of Tracleer be strictly limited pursuant to a Risk Evaluation and Mitigation Strategy ("REMS"). As a matter of law, Actelion must comply with the FDA-mandated REMS program covering Tracleer. Roxane has not addressed this issue. Actelion also has an independent right to decide with whom it will do business and how it will structure its distribution system. Here, Actelion's distribution system is designed to be consistent with its REMS obligations and to protect its intellectual property rights.

Nothing in your letter has changed Actelion's views in this regard, but Actelion is willing to evaluate Roxane's request that it reconsider its position. Among the concerns underlying Actelion's decision not to supply Tracleer samples to Roxane are Actelion's legitimate interests in complying with its REMS program's strict limitations on distribution and protecting its intellectual property. It would therefore help to understand the following:

1. Would Roxane's potential generic formulation infringe Actelion's intellectual property covering Tracleer, including but not limited to United States Patent Number 5,292,740 (the "'740 Patent")? If not, please explain why not.

2. Does Roxane intend to file an ANDA with a Paragraph IV certification, challenging the infringement, validity and/or enforceability of the '740 Patent, and forcing the parties to litigate these issues?

3. Alternatively, does Roxane intend to file a Paragraph III certification, seeking approval only after the '740 Patent expires in November 2015?

Dechert LLP

4. What efforts Roxane has made to acquire samples elsewhere for purposes of BE testing or if Roxane has communicated with the FDA regarding the use of samples acquired outside of the United States for such purposes.

I cannot promise that Roxane's responses to these questions will necessarily change Actelion's position, but Actelion is willing to take them into account in evaluating your request.

Sincerely,

George G. Gordon

George G. Gordon

GGG:jz

EXHIBIT P

KIRKLAND & ELLIS LLP
AND AFFILIATED PARTNERSHIPS

655 Fifteenth Street, N.W.
Washington, D.C. 20005

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Karen N. Walker, P.C.
To Call Writer Directly:
(202) 879-5096
karen.walker@kirkland.com

June 6, 2011

For Settlement Purposes Only
Per Fed. R. Evid. 408

VIA FED EX

Perry Goldman
Vice President, Legal Affairs
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080

Re: *Roxane v. Actelion*

Dear Mr. Goldman:

I have been retained by Roxane Laboratories, Inc. ("Roxane") to represent Roxane in a soon-to-be-filed civil action against Actelion Pharmaceuticals ("Actelion") regarding Roxane's efforts to develop a generic version of Zavesca capsules.

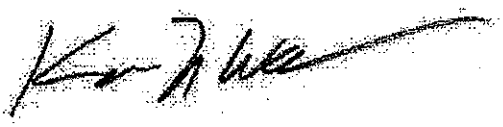
Roxane has been unable to purchase this product, as it normally does in the ordinary course of business, from pharmaceutical wholesalers due to Actelion's restrictions. Accordingly, Roxane has now sent three letters to Actelion, beginning April 19, 2010, requesting to purchase Zavesca capsules (four 90 count cartons) directly from Actelion. Given Actelion's failure to respond to any of these letters, it is clear Actelion is refusing to sell such product to Roxane and Actelion precludes wholesalers from selling such samples to Roxane as well, despite the express prohibition in the FDAAA against using REMS restrictions "to block or delay approval" of generic applications. Upon a review of the facts, it is clear that Actelion's monopolistic and anti-competitive conduct violates Sections 1 and 2 of the Sherman Act as well as applicable state competition and unfair trade practice laws.

Roxane intends to file suit promptly asserting antitrust and related claims against Actelion for its anticompetitive conduct in the market for Zavesca. We will be seeking both injunctive and monetary relief to remedy Actelion's illegal behavior, including compensatory and punitive damages. We anticipate the case will generate substantial attention and activity on

the legislative, regulatory, and litigation fronts as Congress, the FDA and FTC, and class-action lawyers representing direct and indirect purchasers will likely be interested in Roxane's claims.

The purpose of my letter is to propose a meeting to discuss any possible resolution of this dispute prior to filing our complaint. Given the narrow nature of Roxane's initial request -- samples of Zavesca -- we believe it might be in the interests of both companies to resolve the dispute rather than commencing costly and public litigation to resolve the matter.

Sincerely,



Karen N. Walker, P.C.

cc: Andrea J. Kochensparger

EXHIBIT Q

actavis
think smart medicine

VIA UPS

September 6, 2011

Jean-Paul Clozel
Chief Executive Officer
Actelion, Ltd. Gewerbestrasse 16
4123 Allschwil, Switzerland

Re: Purchase Order for Quantities of Tracleer® Necessary to Conduct Analytical and Bioequivalence Studies

Dear Dr. Clozel:

Actavis Elizabeth LLC ("Actavis") wishes to obtain quantities of Actelion's Tracleer® (bosentan) sold in the United States under NDA No. 021290. These quantities are necessary for Actavis to conduct analytical and bioequivalence studies for the purposes of developing a generic version of bosentan.

Specifically, I write to place a purchase request for 4 bottles (60 count each) of Tracleer® 62.5 mg tablets and 17 bottles (60 count each) of 125 mg tablets. Actavis is willing to pay Actelion for the fair market value of these products and to reimburse Actelion for all reasonable shipping, handling and other costs associated with this purchase request. Please let me know what those costs and expense are and provide the details of how best to complete this transaction.

We are aware that the United States Food and Drug Administration ("FDA") conditioned its approval of Tracleer® on a restricted method of distribution providing safeguards regarding Tracleer®'s use. As a result of this restricted distribution program, we are unable to obtain the product from other sources. We are therefore requesting the product directly from Actelion.

Actavis has established and will follow procedures that fully comply with FDA requirements for conducting any required testing involving bosentan. FDA has recognized that study protocols that comply with applicable FDA regulations are an appropriate substitute for the controls present in a restricted access program. Moreover, as the FDA has made clear, restricted access programs implemented to comply with approval conditions imposed pursuant to FDA's authority under Section 505-1 of the Federal Food, Drug and Cosmetic Act ("FDCA"), such as Tracleer®'s, should not be used as a basis for denying another drug manufacturer access to the drug for the purpose of conducting analytical and bioequivalence testing.

Actavis Elizabeth LLC | 200 Elmora Avenue Elizabeth, NJ 07207 | t 908 527-9100 f 908 527-0649

Please respond by September 21, 2011. If we do not hear back from you by that date, we will conclude that Actelion is not willing to proceed with this transaction and will proceed accordingly.

Sincerely,

Tejendra Rao
Senior Director, Sourcing/Purchasing
Actavis Elizabeth, LLC
trao@actavis.com
(980) 659-2640

cc: (VIA EMAIL AND UPS)
Marian Borovsky, Esq., Senior Vice-President and Group General Counsel, Actelion, Ltd.
Terri Nataline, Esq., Vice President, Regulatory and Medical Affairs, Actavis Elizabeth, LLC (nataline@actavis.com)
James Mahanna, Esq., Director, Intellectual Property, Actavis Elizabeth, LLC, (jmahanna@actavis.com)

EXHIBIT R

ACTELION

Tejendra Rao
Senior Director, Sourcing/Purchasing
Actavis Elizabeth LLC
200 Elmora Avenue
Elizabeth, NJ 07207
USA

Allschwil, 20 September 2011

Re: Purchase Order for Quantities of Tracleer® Necessary to Conduct Analytical and Bioquivalence Studies

Dear Dr. Rao,

We have received your letter dated September 8, 2011 on behalf of Actavis Elizabeth LLC ("Actavis"), and considered your inquiry. We disagree with your interpretation of the Food, Drug and Cosmetic Act ("FDCA"). More importantly, nowhere in the FDCA does it require that Actelion relinquish its right to choose with whom it does business. Actelion reserves that right, which exists independently of the restricted distribution program for Tracleer, and has concluded that it will not be fulfilling Actavis' request for Tracleer tablets.

Yours sincerely,

Otto Schwarz
Chief Operating Officer

Dr. Marian Borovsky
Group General Counsel

Actelion Ltd
Gewerbestrasse 16 | CH-4123 Allschwil | Switzerland | phone +41 61 565 65 65 | fax +41 61 565 66 91 | www.actelion.com